Revisión bibliográfica referente al virus de la Influenza A (H1N1).

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- OMS
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Fase actual de alerta de pandemia según la OMS

FASE ACTUAL DE ALERTA EN EL PLAN DE PREPARAOÓN ANTE UNA PANDEMIA DE GRIPE, SEGÚN LA OMS

En la revisión de 2009 de las descripciones de las fases, la OMS ha mantenido la estructuracion en seis fases para facilitar la incorporacionl de nuevas recomendaciones y enfoques a los planes nacionales de preparación y respuesta existentes. Se ha revisado la estructuración y la descripción de las fases de pandemia para facilitar su comprensión, aumentar su precisión y basarlas en fenómenos observables. Las fases 1 a 3 se corresponden con la preparación, en la que se Incluyen las actividades de desarrollo de la capacidad y planificaclón de la respuesta, mientras que las fases 4 a 6 señalan diaramente la necesidad de medidas de respuesta y mltlgacl6n. Además se han elaborado mejor los periodos posteriores a la primera ola pandémica para facilitar las actividades de recuperación pospandémica.

En la actualidad nos encontramos en la fase 5 de alerta de pandemia.

En la naturaleza, los virus gripales circulan continuamente entre los animales, sobre todo entre las aves. Aunque en teoría esos virus podrán convertirse en virus pandémicos, en la fase 1 no hay entre los animales virus circulantes que hayan causado Infecciones humanas.

La fase 2 se caracteriza por la circulación entre los animales domésticos o salvajes de un virus gripal animal que ha causado Infecciones humanas, por lo que se considera una posible amenaza de pandemia.

La fase 3 se caracteriza por la existencia de un virus gripal animal o un virus reagrupado humano - animal que ha causado casos esporádicos o pequeños conglomerados de casos humanos, pero no ha ocasionado una transmisión de persona a persona suficiente para mantener brotes a nivel comunitario. La transmisión limitada de persona a persona puede producirse en algunas circunstancias como, por ejemplo, cuando hay un contacto intimo entre una persona infectada y un cuidador que carezca de protección. Sin embargo, la transmisión limitada en estas circunstancias restringidas no Indica que el virus haya adquirido el nivel de transmisibilidad de persona a persona necesario para causar una pandemia.

La fase 4 se caracteriza por la transmisión comprobada de persona a persona de un virus animal o un virus reagrupado humano-animal capaz de causar "brotes a nivel comunitario", La capacidad de causar brotes sostenidos en una comunidad señala un Importante aumento del riesgo de pandemia. Todo país que sospeche o haya comprobado un evento de este tipo debe consultar urgentemente con la OMS a fin de que se pueda realizar una evaluación conjunta de la situación y el país afectado pueda decidir si se Justifica la puesta en marcha de una operación de contención rápida de la epidemia. La fase 4

señala un Importante aumento del riesgo de pandemia, pero no significa necesariamente que se vaya a producir una pandemia.

La fase 5 se caracteriza por la propagación del virus de persona a persona al menos en dos países de una regl6n de la OMS. Aunque la mayoría de los países no estarán afectados en esta fase, la declaracl6n de la fase 5 es un indicio claro de la inminencia de una pandemia y de que queda poco tiempo para organizar, comunicar y poner en práctica las medidas de mltlgacl6n planificadas,

La fase 6, es decir la fase pandemica, se caracteriza por los criterios que definen la fase 5, acompañados de la aparicion de brotes comunitarios en al menos un tercer pais de una región distinta. La declaración de esta fase indica que está en marcha una pandemia mundial.

En el periodo posterior al de máxima actividad, la Intensidad de la pandemia en la mayoría de los países con una vigilancia adecuada habrá disminuido por debajo de la observada en el momento álgido. En este periodo, la pandemia parece remitir; sin embargo, no pueden descartarse nuevas oleadas, y los países han de estar preparados para una segunda ola.

Las pandemias anteriores se han caracterizado por oleadas de actividad repartidas durarte varios meses. CUando el número de casos disminuye, se requiere una gran habilidad comunicadora para compaginar esa Información con la advertencia de que puede producirse otro ataque, Las olas pandémicas pueden sucederse a Intervalos de meses, y cualquier señal de "relajación" puede resultar prematura.

En el periodo pospandémlco, los casos de gripe habrán vuelto a ser comparables a los habituales de la gripe estacional. Cabe pensar que el virus pandémico se comportará como un virus estacional de tipo A. En esta fase es Importante mantener la vigilancia y actualizar en consecuencia la preparación para una pandemia y los planes de respuesta. Puede requerirse una fase Intensiva de recuperación yevaluacl6n

Noticias de 'a FDA

Autoriza a la FDA de emergencia Uso de Medicamentos de la influenza, los ensayos de diagnóstico de la peste Porcina en respuesta a brote de gripe en humanos

Los EE.UU. Administración de Alimentos y Drogas. En respuesta a peticiones de los EE.UU. Centros para el Control y Prevención de Enfermedades, ha emitido la autorización de emergencia Uso (EUAs) a poner a disposición de la salud pública y el personal médico importante de diagnóstico y terapéuticos para identificar y responder a la peste porcina virus de la gripe en determinadas circunstancias. La agencia publicó esas EUAs por la utilización de determinadas antiviral Tamiflu y Relenza productos, y el Tribunal de Revisión de la gripe porcina-PCR Grupo prueba de diagnóstico.

La UCE autoridad permite la FDA, sobre la base de la evaluación de los datos disponibles, para autorizar el uso no autorizado de los productos médicos o de liquidación o de liquidación usos no autorizados o de aprobado o borrar los productos médicos a raíz de una determinación y la declaración de estado de emergencia, siempre se cumplen ciertos criterios. La autorización final de la declaración de emergencia se rescinde o revoca la autorización por el organismo.

Actualmente, Relenza está aprobado para el tratamiento de enfermedades agudas no complicadas debido a la gripe en adultos y niños mayores de 7 años y que han sido sintomáticos de menos de dos días, y para la prevención de la gripe en adultos y niños de 5 años y más. Tamiflu está aprobado para el tratamiento y la prevención de la gripe en pacientes de 1 año y mayores.

El Tamiflu EUAs permitir también que se utilizarán para tratar y prevenir la gripe en niños menores de 1 211'10, Y para ofrecer recomendaciones de dosificación de suplentes para los nilños mayores de 1 211'10. Además, en virtud de la EUAs, ambos medicamentos pueden ser distribuidos a grandes segmentos de la población sin cumplir los requisitos de etiquetado aplicable a medicamentos dispensados, y acompañado por escrito la información relativa a la emergencia. También pueden ser distribuidos por una gama más amplia de los trabajadores de la salud. Incluidos algunos funcionarios de salud pública y los voluntarios. De conformidad con las leyes estatales y locales y I o respuestas de emergencia de salud pública.

En la autorización de un Tribunal de Revisión de la UCE·PCR gripe porcina Grupo prueba de diagnóstico, la FDA ha determinado que puede ser eficaz en las pruebas de muestras de individuos con diagnóstico de infecciones de gripe A. cuyos subtipos del virus no puede ser identificado por las pruebas disponibles en la actualidad. Esto permite a los EUA el CDC para la distribución de la gripe porcina de ensayo para la salud pública y otros laboratorios que han calificado el equipo necesario y el personal capacitado para realizar e interpretar los resultados.

La prueba amplifica el material gen ético viral a partir de un hisopo nasal o nasofaríngeo. Un resultado positivo indica que el paciente está infectado con la peste porcina presumiblemente virus de la gripe. Pero no la fase de infección. Sin embargo. Un resultado negativo no, por si mismo, excluye la posibilidad de infección por virus de la gripe porcina.

Lo que usted puede hacer para mantenerse saludable

- **Manténgase informado**. Este sitio Web se actualizará periódicamente la información esté disponible.
- La gripe es principalmente para difundir el pensamiento de persona a persona a través de la tos o estornudos de personas infectadas.
- Tomar acciones diarias para mantenerse sano.
    - Cúbrase la nariz y la boca con un pañuelo cuando tosa o estornude. Tire el tejido en la basura después de usarlo.
    - Lávese las manos frecuentemente con agua y jabón. Especialmente después de toser o estornudar. A base de alcohol de limpieza de las manos también son eficaces.
    - Evite tocarse los ojos, la nariz o la boca. Gérmenes propagación de esa manera.
    - Quédese en casa si se enferma. CDC recomienda que permanezca en su casa desde el trabajo o la escuela y limitar el contacto con otro s para evitar infectar a ellos.
- Siga el asesoramiento de salud pública en relación con el cierre de la escuela, evitando aglomeraciones y otras medidas de distanciamiento social.
- Desarrollar un plan de emergencia familiar como medida de precaución. Esto debe incluir el almacenamiento de un suministro de alimentos, medicamentos, visores, alcohol para manos a base de lociones y otros suministros esenciales.

La influenza porcina y usted (gripe porcina)

English: Swine Flu and You – April 23, 2009

¿Qué es la influenza porcina?

La influenza porcina (gripe porcina) es un tipo de influenza que afecta por lo general a los cerdos. Enocasiones, las personas se enferman de influenza porcina. Antes de este reciente brote de influenzaporcina, la mayoría de las personas que se enfermaban con este virus generalmente habían tenidocontacto cercano con los cerdos. Hay ocasiones en las que una persona con influenza porcina puedetransmitirla a alguien más.

¿Hay personas en los EE. UU. que tienen la influenza porcina?

A finales de marzo y principios de abril del 2099, se informó de casos de influenza porcina en personas en los EE. UU. y a nivel internacional. El subtipo específico de la influenza porcina es la influenza tipo A (H1N1). Los CDC y las agencias de salud estatales y locales están trabajando conjuntamente en la investigación de esta situación.

¿Este virus de la influenza porcina se contagia fácilmente?

En la actualidad, el virus de la influenza porcina se está transmitiendo de persona a persona. En este momento, no se sabe con qué facilidad se transmite este virus de una persona a otra.

¿Cuáles son los signos y síntomas de la influenza porcina en las personas?

Los síntomas de la influenza porcina son parecidos a los síntomas de la influenza o gripe estacional. Entre ellos se incluyen fiebre, tos, dolor de cabeza, dolor del cuerpo, dolor de cabeza, escalofríos y cansancio. Algunas personas también pueden tener diarrea y vómito. En años anteriores, algunas personas con la influenza porcina sufrían enfermedades graves (neumonía e insuficiencia respiratoria) o morían. Tal como ocurre con la influencia estacional, la influenza porcina también puede empeorar afecciones médicas existentes.

¿Qué tan grave es la influenza porcina?

Al igual que ocurre con la influenza estacional, la influenza porcina en los seres humanos puede variar de leve a grave. Desde el 2005 hasta febrero del 2009, 12 personas en los EE. UU. contrajeron la influenza porcina. No se reportaron muertes, pero dos personas se enfermaron gravemente. Sin embargo, la influenza porcina puede ser muy grave. En 1988, una mujer embarazada fue hospitalizada en Wisconsin y murió posteriormente debido complicaciones de la influenza porcina. Algunos trabajadores del área de atención médica que cuidaron a esta paciente también resultaron infectados por el virus. Un brote de influenza porcina ocurrido en Nueva Jersey en 1976 enfermó a más de 200 personas y causó la muerte a una persona.

¿Cómo se contrae la influenza porcina?

Usted puede contraer la influenza porcina de dos maneras:

• Por el contacto con cerdos infectados o con superficies contaminadas con los virus de la influenza porcina.

• A través del contacto con una persona que tenga influenza porcina. Es probable que la transmisión de la influenza porcina entre las personas ocurra de la misma forma en que se transmite la influenza estacional.
• Se cree que los nuevos virus de la influenza porcina y los de la influenza estacional se transmiten de persona a persona cuando alguien infectado tose o estornuda.

¿Hay medicamentos para tratar la influenza porcina?
Los CDC recomiendan dos medicamentos antivirales que se expiden con receta médica para tratar o prevenir la influenza porcina. Estos medicamentos son oseltamivir (nombre comercial Tamiflu® o zanamivir (nombre comercial Relenza®). Ambos medicamentos recetados combaten la influenza porcina al evitar que los virus de esta enfermedad se reproduzcan en el cuerpo. Si usted se enferma, estos medicamentos pueden hacer que su enfermedad sea más leve y que usted se sienta mejor en forma más rápida. También pueden ayudar a prevenir que ocurran graves problemas de salud. En relación con el tratamiento, los medicamentos son más eficaces si se inician dentro de los 2 días siguientes a la aparición de la enfermedad.

¿Por cuánto tiempo puede una persona infectada propagar la influenza porcina a otras?
Las personas infectadas por el virus de la influenza porcina pueden transmitir la enfermedad mientras tengan los síntomas (fiebre, tos, dolor de garganta, dolores en el cuerpo, dolor de cabeza, escalofríos y cansancio, y en algunos casos diarrea y vómito) y posiblemente hasta siete días después del inicio de la enfermedad. Los niños, especialmente los más pequeños, podrían ser contagiosos durante periodos más largos.

¿Qué puedo hacer para evitar enfermarme?
En este momento no hay una vacuna contra la influenza porcina. Pero hay medidas que usted puede tomar para ayudar a prevenir la propagación de gérmenes que causan enfermedades respiratorias como la influenza porcina y la influenza estacional. Siga estas medidas a diario para proteger su salud:
• Cúbrase la boca y la nariz con un pañuelo desechable al toser o estornudar. Bote el pañuelo desechable a la basura después de usarlo.
• Lávese las manos a menudo con agua y jabón, especialmente después de toser o estornudar. Los desinfectantes para manos a base de alcohol también son eficaces.
• Trate de no tocarse los ojos, la nariz ni la boca. Esta es la manera en que se propagan los gérmenes.
• Trate de evitar el contacto cercano con personas enfermas.
• Si usted se enferma, los CDC recomiendan que se quede en casa y que no vaya al trabajo o a la escuela. No se acerque mucho a otras personas para evitar contagiarlas.

¿Qué debo hacer si me enfermo?
Comuníquese con su proveedor de atención médica si usted vive en un área donde se hayan identificado casos de infecciones por influenza porcina en personas y se enfermar con síntomas parecidos a los de la influenza (entre ellos, fiebre, dolor del cuerpo, secreciones de la nariz, dolor de garganta,

náusea o vómito o diarrea). El proveedor de atención médica decidirá si hace falta realizar pruebas para detectar la influenza o si necesita que le hagan tratamiento.

Si está enfermo, se debe quedar en casa y evitar el contacto con otras personas tanto como sea posible para evitar propagar su enfermedad a otros.

Si se enferma y presenta alguno de los siguientes signos de advertencia, busque atención médica de inmediato.

En los niños, los principales signos de emergencia que requieren atención médica inmediata son:

• Respiración agitada o dificultad para respirar.
• Color azulado en la piel.
• Que el niño no esté tomando suficientes líquidos.
• El niño no quiere despertarse ni interactuar con los otros.
• Que el niño esté tan molesto que no quiera que lo carguen.
• Los síntomas similares a los de la influenza o gripe mejoran pero luego regresan con fiebre y una tos peor.
• Fiebre con sarpullido.

En los adultos, los principales signos de advertencia que requieren atención médica de emergencia son:

• Dificultad para respirar o se queda sin aliento.
• Dolor o presión en el pecho o el abdomen.
• Mareo repentino.
• Confusión.
• Vómitos fuertes o constantes.

¿Me puede dar influenza porcina por comer o cocinar carne de cerdo?
No. La influenza porcina no se encuentra en los alimentos. Usted no puede contraer la influenza porcina por comer carne de cerdo o sus productos derivados. No hay riesgos si se come carne de cerdo y sus derivados que han sido manipulados y cocinados de manera adecuada.

Datos importantes sobre la influenza porcina (gripe porcina)

¿Qué es la influenza porcina?

La influenza porcina (gripe porcina) es una enfermedad respiratoria de los cerdos causada por el virus de la influenza tipo A, el cual provoca brotes comunes de influenza entre estos animales. Los virus de la influenza porcina enferman gravemente a los cerdos pero las tasas de mortalidad son bajas.

Estos virus pueden propagarse entre los cerdos durante todo el año, pero la mayoría de los brotes infecciosos ocurren en los meses finales del otoño e invierno, al igual que los brotes en las personas. El virus de la influenza porcina clásico (virus de la influenza H1N1 tipo A) fue aislado por primera vez de un cerdo en 1930.

¿Cuántos virus de la influenza porcina hay?

Al igual que todos los virus de la influenza, los virus de la influenza porcina cambian de manera constante. Los cerdos pueden estar infectados por los virus de la influenza aviar y humana, así como también por los virus de la influenza porcina. Cuando los virus de la influenza de otras especies infectan a los cerdos, los virus pueden reagruparse (es decir cambiar sus genes) y pueden surgir nuevos virus de la mezcla de los virus de la gripe porcina con los de la gripe humana o aviar. A través de los años, han surgido diferentes variaciones de los virus de la influenza porcina. En la actualidad, hay cuatro subtipos principales del virus de la influenza tipo A aislados de cerdos: H1N1, H1N2, H3N2 y H3N1. Sin embargo, la mayoría de los virus de la influenza aislados recientemente de cerdos han sido los virus H1N1.

Influenza porcina en seres humanos

¿Los seres humanos pueden contagiarse de influenza porcina?

Los virus de la influenza porcina por lo general no infectan a los seres humanos. Sin embargo, han ocurrido casos esporádicos de infecciones de influenza porcina en seres humanos. Por lo general, estos casos se presentan en personas que tienen exposición directa a los cerdos (es decir, niños que se acercan a los cerdos en ferias o trabajadores de la industria porcina). Además, ha habido algunos casos documentados de personas que han contagiado el virus de la influenza porcina a otras. Por ejemplo, en 1988, un presunto brote infeccioso de influenza porcina en cerdos en Wisconsin causó múltiples infecciones en seres humanos y, aunque no ocurrió un brote en la comunidad, se identificaron anticuerpos que comprobaron la transmisión del virus de un paciente a personal de atención médica que habían tenido contacto cercano con él.

¿Con qué frecuencia se registran infecciones de influenza porcina en seres humanos?

En el pasado, los CDC recibían notificaciones de aproximadamente un caso de infección por el virus de la influenza porcina en seres humanos cada uno o dos años en los Estados Unidos; sin embargo, de diciembre del 2005 a febrero del 2009 se han reportado 12 casos de infecciones por influenza porcina en personas.

¿Cuáles son los síntomas de la influenza porcina en los seres humanos?

Los síntomas de la influenza porcina en las personas son similares a los de la influenza estacional común en seres humanos y entre estos se incluyen fiebre, letargo, falta de apetito y tos. Algunas personas con influenza porcina han reportado también secreciones nasales, dolor de garganta, náuseas, vómitos y diarrea.

¿Las personas pueden contraer influenza porcina por comer carne de cerdo?

No. Los virus de la influenza porcina no se transmiten por los alimentos. Usted no puede contraer influenza porcina por comer carne de cerdo o sus productos derivados. No hay riesgos si se come carne de cerdo y sus derivados que han sido manipulados y cocinados de manera adecuada. Si se cocina la carne de cerdo a una temperatura interna de aproximadamente 71° C (160° F), se eliminan los virus de la influenza porcina, como también otras bacterias y virus.

¿Cómo se propaga la influenza porcina?

Los virus de la influenza se pueden transmitir directamente de los cerdos a las personas y de las personas a los cerdos. Las infecciones en seres humanos por los virus de la influenza provenientes de los cerdos tienen más probabilidad de ocurrir en las personas que están en contacto cercano con cerdos infectados, como las que trabajan en criaderos de cerdos y las que participan en las casetas de cerdos en las ferias de exhibiciones de animales de cría. La transmisión de la influenza porcina de persona a persona también puede ocurrir. Se cree que esta transmisión es igual a la de la influenza estacional en las personas, es decir principalmente de persona a persona cuando las personas infectadas por el virus de la influenza tosen o estornudan. Las personas pueden infectarse al tocar algo que tenga el virus de la influenza y luego llevarse las manos a la boca o la nariz.

¿Qué información tenemos sobre la transmisión de la influenza porcina de persona a persona?

En septiembre de 1988, una mujer embarazada sana de 32 años de edad fue hospitalizada por pulmonía y falleció 8 días después. El virus de la influenza porcina H1N1 fue detectado. Cuatro días antes de enfermarse, la paciente había visitado una exhibición de cerdos en una feria del condado donde se registraba una enfermedad seudogripal generalizada entre los cerdos.

En estudios de seguimiento, el 76% de los expositores de cerdos a los cuales se les realizaron pruebas presentaron anticuerpos que comprobaron infección por influenza porcina, aunque en este grupo no se detectaron enfermedades

graves. Estudios adicionales indicaron que de uno a tres empleados del personal de atención médica que habían tenido contacto con la paciente presentaron enfermedad seudogripal leve y anticuerpos contra la infección de la influenza porcina.

¿Cómo se diagnostican las infecciones por influenza porcina en seres humanos?

Para diagnosticar una infección por influenza porcina tipo A, por lo general se debe recoger una muestra de secreción del aparato respiratorio entre los primeros 4 a 5 días de aparecida la enfermedad (cuando una persona infectada tiene más probabilidad de diseminar el virus). Sin embargo, algunas personas, especialmente los niños, pueden propagar el virus durante 10 días o más. Para la identificación del virus de la influenza porcina tipo A es necesario enviar la muestra a los CDC para que se realicen pruebas de laboratorios.

¿Qué medicamentos existen para tratar a las personas con infecciones por influenza porcina?

Existen cuatro medicamentos antivirales diferentes que están autorizados en los Estados Unidos para el tratamiento de la influenza: amantadina, rimantadina, oseltamivir y zanamivir. Aunque la mayoría de los virus de la influenza porcina han sido sensibles a los cuatro tipos de medicamentos, los siete virus más recientes de la influenza porcina asilados de personas son resistentes a la amantadina y la rimantadina. En la actualidad, los CDC recomiendan el uso de oseltamivir o zanamivir para la prevención y el tratamiento de la infección por los virus de la influenza porcina. Consulte más información sobre las recomendaciones para el tratamiento.

¿Qué otros casos de brotes de influenza porcina hay?

Probablemente el caso más conocido sea el brote de influenza porcina entre los soldados de Fort Dix, Nueva Jersey, en 1976 . Este virus causó pulmonía, demostrada mediante radiografías, a por lo menos 4 soldados y 1 muerte; todos estos pacientes anteriormente gozaban de buena salud. El virus se transmitió a contactos cercanos en un ambiente de entrenamiento básico, y no ocurrió transmisión afuera del grupo de entrenamiento básico. Se cree que el virus permaneció en ese lugar un mes y desapareció. Se desconocen la fuente del virus, la fecha exacta de su ingreso a Fort Dix, los factores que limitaron su transmisión y su duración. El brote de Fort Dix pudo haber sido causado por el ingreso de un virus de un animal a una población humana bajo estrés en contacto cercano con instalaciones saturadas de gente y durante el invierno. El virus de la influenza porcina tipo A recogido de un soldado de Fort Dix fue bautizado A/New Jersey/76 (Hsw1N1).

¿El virus de la influenza porcina H1N1 es igual a los virus H1N1 de la influenza en seres humanos?
No. Los virus de la influenza porcina H1N1 son antigénicamente muy diferentes de los virus H1N1 de los seres humanos, por consiguiente las vacunas de la influenza estacional para las personas no proporcionan protección contra los virus de la influenza porcina H1N1.

Influenza porcina en cerdos

¿Cómo se propaga la influenza porcina entre los cerdos?

Se cree que los virus de la influenza porcina se transmiten principalmente mediante el contacto cercano entre cerdos y posiblemente mediante objetos contaminados que se mueven entre los cerdos infectados y sanos. Las manadas de cerdos con continuas infecciones de influenza porcina y las manadas que son vacunadas contra esta enfermedad pueden enfermarse de manera esporádica, pueden ser asintomáticas o solo presentar síntomas leves de la infección.

¿Cuáles son los signos de la influenza porcina en los cerdos?

Los signos de la influenza porcina puede ser la aparición súbita de fiebre, depresión, tos (gruñido), secreciones de la nariz y los ojos, estornudos, dificultad para respirar, enrojecimiento o inflamación de ojos y pérdida del interés en la comida.

¿Qué tan frecuente es la influenza porcina entre los cerdos?

Los virus de la influenza porcina H1N1 y H3N2 son endémicos entre las poblaciones de cerdos en los Estados Unidos y es una situación que la industria aborda de manera habitual. Los brotes entre los cerdos se presentan por lo general en los meses de temperaturas frías (finales del otoño y el invierno) y a veces con el ingreso de nuevos cerdos a manadas vulnerables. Los estudios han demostrado que la influenza porcina H1N1 es común entre las poblaciones de cerdos de todo el mundo y que un 25 por ciento de los animales presentan evidencia de anticuerpos de la infección. Los estudios en los Estados Unidos han demostrado que el 30 por ciento de la población de los cerdos sometidos a pruebas han presentado evidencia de anticuerpos por la infección H1N1. Para ser más precisos, se ha comprobado la presencia de los anticuerpos de la infección H1N1 en el 51 por ciento de los cerdos en el norte de la región central de los Estados Unidos. Las infecciones en las personas por los virus H1N1 de la influenza porcina son poco comunes. En la actualidad, no hay forma de diferenciar en los cerdos los anticuerpos producidos en reacción a la vacunación de los anticuerpos generados ante las infecciones por influenza porcina H1N1.

Aunque los virus de la influenza porcina H1N1 se han encontrado en las poblaciones de cerdos desde por lo menos 1930, los virus de la influenza porcina H3N2 no comenzaron a presentarse entre los cerdos en los Estados Unidos hasta 1998. Los virus H3N2 inicialmente ingresaron a las poblaciones de cerdos por los humanos. Los virus actuales de la influenza porcina H3N2 están estrechamente asociados a los virus H3N2 de los seres humanos.

¿Hay alguna vacuna para la influenza porcina?

Existen vacunas que se administran a los cerdos para la prevención de la influenza porcina. Sin embargo, no hay una vacuna para proteger a las personas contra la influenza porcina. Es posible que la vacuna contra la influenza estacional proporcione protección parcial contra los virus H3N2, pero no contra los virus H1N1 de la influenza porcina.

Influenza H1N1 (gripe porcina)

Los CDC siguen tomando medidas intensas para responder al creciente brote causado por el virus nuevo de la influenza H1N1.

Los objetivos de la respuesta de los CDC son:

1. Reducir la transmisión y la intensidad de la enfermedad y
2. Proporcionar información para ayudar a los proveedores de atención médica, los funcionarios de salud pública y al público en general a enfrentar los desafíos que representa esta emergencia.

Los CDC siguen publicando y actualizando diariamente las directrices provisionales en respuesta a esta situación que está cambiando constantemente. Los CDC darán a conocer directrices provisionales actualizadas para los médicos sobre cómo identificar y atender a las personas que están enfermas con el virus nuevo de la influenza H1N1. Estas recomendaciones asignarán prioridades para la realización de pruebas y el tratamiento de la infección con el virus nuevo de la influenza H1N1. La prioridad en el uso de los medicamentos antivirales contra la influenza durante este brote será para tratar a las personas con complicaciones graves causadas por la influenza.

El 3 de mayo, los CDC tienen programado completar la movilización del 25 por ciento de los suministros de la División de la Reserva Estratégica Nacional (*Strategic National Stockpile* o SNS) a todos los estados del territorio continental de los Estados Unidos. Estos suministros y medicamentos ayudarán a los estados y a los territorios de los EE. UU. a responder a este

brote. Además, el Gobierno Federal y las compañía farmacéuticas fabricantes de vacunas han empezado el proceso de creación de una vacuna contra el virus nuevo de la influenza H1N1.

Las acciones de respuesta son intensas, pero pueden variar en los distintos estados o comunidades según las circunstancias locales. Las comunidades, los negocios, los sitios de congregación religiosa, las escuelas y las personas pueden tomar medidas para disminuir la transmisión de este brote. A las personas que están enfermas se les insta a que permanezcan en casa y no vayan al trabajo o a la escuela para evitar el contacto con otras personas, excepto cuando tengan que ir a consulta médica. Esta medida puede evitar una mayor propagación de la enfermedad.

Casos de influenza H1N1 (gripe porcina) en seres humanos en los EE. UU.

Hasta el 4 de mayo de 2009 a las 11:00 a.m. hora del Este

Estados	# de casos confirmados mediante pruebas de laboratorio	Muertes
Alabama	4	
Arizona	17	
California	49	
Colorado	6	
Connecticut	2	
Delaware	20	
Florida	5	
Georgia	1	
Idaho	1	
Illinois	82	
Indiana	3	
Iowa	1	
Kansas	2	
Kentucky*	1	
Louisiana	7	
Maine	1	
Maryland	4	
Massachusetts	6	
Michigan	2	
Minnesota	1	
Missouri	1	
Nebraska	1	
Nevada	1	
New Hampshire	1	
New Jersey	6	
New Mexico	1	
New York	90	
North Carolina	1	
Ohio	3	

Oregon	15	
Pennsylvania	1	
Rhode Island	1	
South Carolina	16	
Tennessee	2	
Texas	41	1
Utah	1	
Virginia	3	
Wisconsin	3	
NÚMERO TOTAL (36)	**403 casos**	**1 muerte**

Casos de influenza porcina en seres humanos a nivel internacional
consulte: Organización Mundial de la Salud

*El caso es residente de Kentucky pero se encuentra hospitalizado en Georgia

Gripe porcina

Señoras y señores:

Sobre la base de la evaluación de todas las informaciones disponibles, y después de realizar varias consultas con expertos, he decidido elevar el nivel de alerta de pandemia de gripe desde la actual fase 4 a la fase 5.

Es necesario tomarse muy en serio las pandemias de gripe precisamente por la capacidad que tienen para propagarse con rapidez a todos los países del mundo.

Un aspecto positivo es que ahora el mundo está mejor preparado para afrontar una pandemia de gripe que nunca antes a lo largo de la historia.

Las medidas de preparación adoptadas a raíz de la amenaza de la gripe aviar por H5N1 han sido una inversión, y ahora estamos obteniendo los beneficios.

Por primera vez en la historia podemos seguir la evolución de una pandemia en tiempo real.

Doy las gracias a los países que están poniendo los resultados de sus investigaciones a disposición del público. Ello nos facilita la comprensión de la enfermedad.

Estoy impresionada por la labor que están realizando los países afectados al afrontar los brotes en curso.

Asimismo, quiero dar las gracias a los Gobiernos de los Estados Unidos y del Canadá por el apoyo que prestan a la OMS, y a México.

Permítanme recordarles que, por definición, las enfermedades nuevas se conocen mal. Es notorio que los virus de la gripe mutan rápidamente y se comportan de forma impredecible.

La OMS y las autoridades sanitarias de los países afectados no tendrán todas las respuestas inmediatamente, pero las obtendremos.

La OMS seguirá de cerca la pandemia a escala epidemiológica, clínica y virológica.

Los resultados de esas evaluaciones continuas se publicarán en forma de asesoramiento en materia de salud pública, y se pondrán a disposición general.

Todos los países deberían activar de inmediato sus planes de preparación para una pandemia. Los países deberían mantenerse en alerta ante posibles brotes inusuales de síndromes gripales y de neumonías graves.

En estos momentos, las medidas eficaces y esenciales son la elevación de la vigilancia, la detección y el tratamiento precoces, y el control de la infección en todos los centros de salud.

El paso a una fase superior de la alerta es una señal a los gobiernos, los ministerios de salud y a otros ministerios, al sector farmacéutico y al mundo empresarial de que ahora se deberían adoptar determinadas medidas de forma cada vez más urgente, y a un ritmo acelerado.

Me he puesto en contacto con países donantes, con el UNITAID, la alianza GAVI, el Banco Mundial y otras instancias para movilizar recursos.

Me he puesto en contacto con empresas fabricantes de medicamentos antivirales para evaluar la capacidad y todas las opciones para aumentar la producción.

También me he puesto en contacto con fabricantes de vacunas que pueden contribuir a la producción de una vacuna contra la pandemia.

El mayor interrogante ahora mismo es: ¿qué magnitud va a tener la pandemia, en particular ahora en sus inicios?

Es posible que las manifestaciones clínicas de la enfermedad abarquen desde las afecciones leves hasta los casos graves. Hemos de seguir vigilando la

evolución de la situación para obtener las informaciones y datos específicos que necesitamos para responder a esa pregunta.

Sabemos también, por experiencias pasadas, que la gripe puede causar afecciones leves en los países ricos y enfermedades más graves, con una elevada mortalidad, en los países en desarrollo.

Cualquiera que sea la situación, la comunidad internacional debería considerar estos momentos como una oportunidad idónea para mejorar significativamente la preparación y respuesta.

Ante todo, es una oportunidad para la solidaridad mundial en la búsqueda de respuestas y soluciones que beneficien a todos los países, a la humanidad entera. Ciertamente, es la humanidad entera lo que está amenazado durante una pandemia.

Como he dicho, ahora mismo no tenemos todas las respuestas, pero las obtendremos.

Muchas gracias.

ACTUALIDAD - GRIPE POR A (H1N1)

30 de abril de 2009 -- A partir de hoy, la OMS se referirá al nuevo virus de la gripe utilizando la denominación virus gripal A(H1N1).

Se eleva el nivel de alerta de pandemia de gripe desde la actual fase 4 a la fase 5

29 de abril de 2009 - Sobre la base de la evaluación de todas las Informadores disponibles, y después de realizar varias consultas con expertos, la Directora General de la OMS ha decidido elevar el nivel de alerta de pandemia de gripe desde la fase 4 a la fase 5.

La Directora General hizo hincapié en que en estos momentos las medidas eficaces y esenciales son la elevación de la vigilancia, la detección y el tratamiento precoces, y el control de la Infección en todos los centros de salud.

Directrices provisionales para el control de infecciones y recomendaciones para el uso de medicamentos antivirales en pacientes con infección presunta o confirmada por influenza porcina tipo A (H1N1) y en personas que hayan tenido contacto cercano con ellos

Objetivo: Proporcionar directrices provisionales sobre el uso de medicamentos antivirales para el tratamiento y la quimioprofilaxis de la infección por el virus de la influenza porcina tipo A (H1N1). Estas guías incluyen su uso en pacientes con infección presunta o confirmada por el virus de la influenza tipo A (H1N1) y personas que han tenido contacto cercano con estos pacientes.

Definiciones de caso

Un *caso confirmado* de infección por el virus de la influenza porcina tipo A (H1N1) se define como una persona con enfermedad respiratoria aguda y una infección por el virus de la influenza porcina tipo A (H1N1) confirmada por un laboratorio de los CDC a través de una o más de las pruebas siguientes:

1. método RT-PCR en tiempo real
2. cultivo viral

Periodo infeccioso

El periodo infeccioso para un caso confirmado de infección por el virus de la influenza porcina tipo A (H1N1) se define como el periodo que abarca desde el día anterior a la aparición de la enfermedad hasta los 7 días posteriores a la aparición de la enfermedad.

Un ***presunto caso*** de infección por el virus de la influenza tipo A (H1N1) se define como:

1) una persona con una enfermedad respiratoria aguda que fue un contacto cercano de un caso confirmado de infección por el virus de la influenza porcina tipo A (H1N1) durante el periodo infeccioso del caso o

2) una persona con una enfermedad respiratoria aguda que viajó o reside en un área en donde se han presentado casos confirmados de infecciones por el virus de la influenza porcina A (H1N1).

Un ***contacto cercano*** se define como: haber estado a unos 2 metros (6 pies) o menos de una persona enferma que tiene un caso presunto o confirmado de infección por el virus de la influenza porcina tipo A (H1N1), durante el periodo infeccioso de la enfermedad.

Una ***enfermedad respiratoria aguda*** se define como: la aparición reciente de al menos dos de los siguientes síntomas: rinorrea o congestión nasal, dolor de garganta, tos (con o sin fiebre o febrícula)

Un ***grupo de alto riesgo de sufrir complicaciones por la influenza*** se define como: una persona que tiene un alto riesgo de sufrir complicaciones por la influenza estacional (ver en ingles). Sin embargo, es muy pronto para establecer qué personas tienen un alto riesgo de sufrir complicaciones debido a la infección por el virus de la influenza porcina tipo A (H1N1). Estas directrices se actualizarán tan pronto se disponga de nueva información.

Los médicos deben considerar la posibilidad de infección por el virus de la influenza porcina tipo A (H1N1) en el diagnóstico diferencial de pacientes con enfermedad respiratoria febril y que: 1) vivan en áreas de los Estados Unidos en las que se han presentado casos confirmados de infección por el virus de la influenza porcina tipo A (H1N1) o 2) hayan viajado recientemente a México o hayan tenido contacto directo con personas que tengan una enfermedad respiratoria febril y que en los 7 días anteriores a la aparición de la enfermedad estuvieron en áreas de los Estados Unidos o México en las que se hayan presentado casos confirmados de infecciones por influenza porcina.

Consideraciones especiales para los niños

No se debe suministrar aspirina o productos que contengan aspirina (p. ej. subsalicilato de bismuto – Pepto Bismol) a ningún caso presunto o confirmado de infección por el virus de la influenza porcina tipo A (H1N1) que tenga 18 años o menos de edad debido al riesgo de sufrir el síndrome de Reye. Para aliviar la fiebre, se recomienda el uso de otros medicamentos antipiréticos como el acetaminofeno (paracetamol) o medicamentos antiinflamatorios no esteroides.

Resistencia antiviral

Este virus de la influenza **porcina** tipo A (H1N1) es sensible (susceptible) a los medicamentos antivirales inhibidores de la neuraminidasa: zanamivir y oseltamivir. Es resistente a los medicamentos antivirales del grupo adamantane: amantadina y rimantadina.

Los virus de la influenza estacional A y B continúan circulando en los Estados Unidos y México a bajos niveles. Los virus de la influenza **humana** tipo A

(H1N1) que están en circulación en la actualidad son resistentes al oseltamivir y sensibles (susceptibles) al zanamivir, la amantadina y la rimantadina. Los virus de la influenza **humana** tipo A (H3N2) son resistentes a la amantadina y rimantadina, pero sensibles (susceptibles) al oseltamivir y zanamivir. Por lo tanto, en estos momentos las recomendaciones para el tratamiento antiviral de casos presuntos de infección por el virus de la influenza porcina tipo A (H1N1) requieren que se tenga en cuenta la posible infección por el virus de la influenza **porcina** tipo A (H1N1) al igual que por los virus de la influenza **humana** y sus diferentes susceptibilidades antivirales.

Tratamiento antiviral

Presuntos casos

Se recomienda el tratamiento antiviral empírico para cualquier persona enferma que se ***presuma*** está infectada por el virus de la influenza porcina tipo A (H1N1). El tratamiento antiviral ya sea solo con zanamivir o con una combinación de oseltamivir y amantadina o rimantadina debe iniciarse tan pronto sea posible después de la aparición de la enfermedad. La duración recomendada del tratamiento es cinco días. Las recomendaciones para el uso de antivirales pueden cambiar si se recibe nueva información sobre susceptibilidades antivirales. ***La dosificación y la programación de las dosis recomendadas para el tratamiento de la infección por el virus de la influenza porcina tipo A (H1N1) son las mismas que las recomendadas para la influenza estacional****: (ver en inglés)*

Casos confirmados

Para el tratamiento antiviral de un caso confirmado de infección por el virus de la influenza porcina tipo A (H1N1) se pueden administrar ya sea oseltamivir o zanamivir. La duración recomendada del tratamiento es cinco días. Se deben considerar recetar estos mismos medicamentos antivirales para el tratamiento de casos cuyas pruebas resulten positivas a la influenza A pero negativas a los virus de la influenza estacional H3 y H1 por el método PCR.

Mujeres embarazadas

Los medicamentos oseltamivir, zanamivir, amantadina y rimantadina se consideran "medicamentos de categoría C" cuando son utilizados durante el embarazo, lo que significa que no se han realizado estudios clínicos para evaluar su inocuidad en mujeres embarazadas. Se han reportado solamente dos casos de uso de amantadina para la influenza grave durante el tercer trimestre de embarazo. Sin embargo, se ha demostrado en estudios en animales que la amantadina y rimantadina son medicamentos teratogénicos y embriotóxicos si se administran en dosis considerablemente altas. Debido a

que se desconocen los efectos de los medicamentos antivirales para la influenza en las mujeres embarazadas y sus fetos, estos cuatro medicamentos, deben usarse durante el embarazo solamente si los beneficios potenciales justifican el riesgo para el embrión o feto; se debe consultar la literatura médica que incluye el fabricante del producto en el empaque. Sin embargo, no se han reportado efectos adversos en mujeres que recibieron oseltamivir o zanamivir durante el embarazo o en sus bebés.

Quimioprofilaxis antiviral

Para la quimioprofilaxis antiviral de la infección por el virus de la influenza porcina tipo A (H1N1) se recomienda el uso de oseltamivir o zanamivir. La duración de la quimioprofilaxis antiviral es de 7 días después de la última exposición conocida a un caso confirmado de infección por el virus de la influenza porcina tipo A (H1N1). ***La dosificación y la programación de las dosis recomendadas para la quimioprofilaxis de la infección por el virus de la influenza porcina tipo A (H1N1) son las mismas que la recomendada para la influenza estacional:*** *(ver en inglés)*

La quimioprofilaxis antiviral (preexposición o posexposición) con oseltamivir o zanamivir se ***recomienda*** para las siguientes personas:

1. Contactos cercanos que viven en la misma casa y han tenido contacto con un caso de infección presunta o confirmada y que tienen un riesgo alto de sufrir complicaciones por la influenza (aquellas con ciertas afecciones crónicas, ancianos).
2. Niños en edad escolar que tienen un riesgo alto de sufrir complicaciones por la influenza (los que tienen ciertas afecciones crónicas) y que han tenido contacto cercano (cara a cara) con un caso de infección presunta o confirmada.
3. Personas que viajan a México y tienen un alto riesgo de sufrir complicaciones por la influenza (personas con ciertas afecciones crónicas, ancianos).
4. Personas que trabajan en la frontera con México y tienen un alto riesgo de sufrir complicaciones por la influenza (personas con ciertas afecciones crónicas, ancianos).
5. Personal de cuidado de la salud y trabajadores de salud pública que tuvieron contacto cercano, sin medidas de protección, con un caso de infección confirmada por el virus de la influenza porcina tipo A (H1N1) durante el periodo infeccioso de la persona.

Se puede ***considerar*** realizar la quimioprofilaxis antiviral (preexposición o posexposición) con oseltamivir o zanamivir en las siguientes personas:

1. Cualquier personal del cuidado de la salud que tiene un alto riesgo de sufrir complicaciones por la influenza (personas con ciertas afecciones crónicas, ancianos) que esté trabajando en un área en que se han

confirmado casos de influenza porcina tipo A (H1N1) y que esté al cuidado de pacientes con cualquier enfermedad respiratoria febril.

2. Personas que no tienen alto riesgo que viajan a México, personal de socorro inmediato o quienes trabajan en la frontera, y que laboran en áreas con casos confirmados de infecciones por el virus de la influenza porcina tipo A (H1N1).

Tabla 1. La gripe porcina de origen las recomendaciones de dosificación de medicamentos antivirales.

Agente del grupo		Tratamiento	Quimioprofilaxis
Oseltamivir			
Adultos		75-mg cápsulas dos veces al día durante 5 días	75-mg cápsula una vez al día
Niños (edad, 12 meses o más de edad), peso:	15 kg o menos	60 mg por día dividido en 2 dosis	30 mg una vez al día
	15ta-23ra kg	90 mg por día dividido en 2 dosis	45 mg una vez al día
	24-40 kg	120 mg por día dividido en 2 dosis	60 mg una vez al día
	> 40 kg	150 mg por día dividido en 2 dosis	75 mg una vez al día
Zanamivir			
Adultos		Dos inhalaciones de 5 mg (10 mg en total) dos veces al día	Dos inhalaciones de 5 mg (10 mg en total) una vez al día
Niños pequeños		Dos inhalaciones de 5 mg (10 mg en total) dos veces al día (edad, 7 años de edad o más)	Dos inhalaciones de 5 mg (10 mg en total) una vez al día (edad de 5 años o más)

Niños menores de 1 año

Niños menores de un año de edad corren un alto riesgo de complicaciones de la gripe humana estacional de infección por el virus. Las características de las infecciones humanas con la peste porcina origen virus H1N1 todavía se están estudiando, y no se sabe si los niños están en mayor riesgo de complicaciones asociadas con la peste porcina origen infección por H1N1 en comparación con niños mayores y adultos. Limitada de datos de seguridad sobre el uso de oseltamivir (o zanamivir) están disponibles en niños menores de un año de edad, y el oseltamivir no es licencia para su uso en niños menores de 1 año de edad. Los datos disponibles provienen de la utilización de oseltamivir para el tratamiento de la gripe estacional. Estos datos sugieren que los efectos adversos graves son poco frecuentes, y la Sociedad de Enfermedades Infecciosas de América señaló recientemente, en relación con el uso de oseltamivir en niños menores de 1 año de edad con la gripe estacional, que "… los datos retrospectivos limitados sobre la seguridad y la eficacia de oseltamivir en este grupo de edad de los jóvenes no han demostrado por edad de la toxicidad de drogas atribuible a la fecha. "

Dado que los bebés suelen tener altas tasas de morbilidad y mortalidad de la gripe, los bebés con la peste porcina origen la gripe A (H1N1), las infecciones pueden beneficiarse de tratamiento con oseltamivir.

Cuadro 2. Recomendaciones de dosificación para el tratamiento antiviral de los niños menores de 1 año con oseltamivir.

Edad	El tratamiento recomendado de dosis durante 5 días
<3 meses	12 mg dos veces al día
3-5 meses	20 mg dos veces al día
6-11 meses	25 mg dos veces al día

Cuadro 3. Recomendaciones de dosificación para la quimioprofilaxis antiviral de los niños menores de 1 año con oseltamivir.

Edad	Recomienda la profilaxis de dosis para 10 días
<3 meses	No se recomienda a menos que la situación juzgado crítica debido a la escasez de datos relativos a su uso en este grupo de edad
3-5 meses	20 mg una vez al día
6-11 meses	25 mg una vez al día

Proveedores de servicios de salud deben ser conscientes de la falta de datos sobre la seguridad y la dosificación de la hora de considerar el uso de oseltamivir en una joven de lactantes gravemente enfermos con origen confirmado la peste porcina o la gripe H1N1 que ha sido expuesto a la peste porcina H1N1 confirmado un caso, un atento seguimiento de los lactantes y los eventos adversos cuando oseltamivir se utiliza.

Mujeres Embarazadas

Oseltamivir y el zanamivir son “Embarazo Categoría C”, los medicamentos, lo que indica que los estudios clínicos no se han llevado a cabo para evaluar la seguridad de estos medicamentos para las mujeres embarazadas. Debido a los efectos no conocidos de la gripe medicamentos antivirales en las mujeres embarazadas y sus fetos, oseltamivir o zanamivir debe utilizarse durante el embarazo sólo si el beneficio potencial justifica el riesgo potencial para el embrión o feto, de los fabricantes el prospecto debe ser consultado. Sin embargo, no hubo efectos adversos se han notificado entre las mujeres que recibieron oseltamivir o zanamivir durante el embarazo o los niños nacidos de mujeres que recibieron oseltamivir o zanamivir. El embarazo no deben considerarse una contraindicación para el uso de oseltamivir o zanamivir. Debido a su actividad sistémica, el oseltamivir es preferido para el tratamiento de mujeres embarazadas. La droga de elección para la profilaxis es menos

clara. Zanamivir puede ser preferible debido a su limitada absorción sistémica, sin embargo, complicaciones respiratorias que pueden estar asociados con zanamivir inhalado por su la vía de administración deben ser considerados, especialmente en mujeres en riesgo de problemas respiratorios.

Eventos adversos y Contraindicaciones

Zanamivir (Relenza)

Se dispone de datos limitados sobre la seguridad o la eficacia de zanamivir para personas con enfermedad respiratoria subyacente, o para las personas con graves complicaciones de la gripe, y el zanamivir sólo tiene licencia para su uso en las personas sin enfermedad cardiaca o respiratoria. En un estudio de tratamiento de zanamivir ILI entre las personas con asma o enfermedad pulmonar obstructiva crónica en la que se administró la medicación de estudio después de su uso de un agonista B2-, el 13% de los pacientes que recibieron zanamivir y el 14% de los pacientes que recibieron placebo (lactosa en polvo inhalado vehículo) experimentaron un mayor descenso del 20% en el volumen espiratorio forzado en 1 segundo (VEF1) después del tratamiento. Sin embargo, en un estudio fase I de las personas con asma leve o moderada que no han ILI, uno de los 13 pacientes presentaron broncoespasmo después de la administración de zanamivir. Además, durante la vigilancia postcomercialización, los casos de deterioro de la función respiratoria después de la inhalación de zanamivir se ha informado. Dado el riesgo de eventos adversos graves y porque la eficacia no se ha demostrado en esta población, zanamivir no se recomienda para el tratamiento de pacientes con enfermedad de las vías respiratorias. Reacciones alérgicas, incluyendo orofaríngea o edema facial, también se han notificado durante la vigilancia posterior.

En estudios clínicos de tratamiento de las personas con la gripe sin complicaciones, la frecuencia de eventos adversos fueron similares para las personas que reciben zanamivir inhalado y para los que recibieron placebo (es decir, la lactosa inhalada solo vehículo). Los eventos adversos más comunes reportados por ambos grupos fueron diarrea, náuseas, sinusitis, los signos y síntomas nasales, bronquitis, tos, dolor de cabeza, mareos y oído, nariz y garganta.

Cada uno de estos síntomas se informó en menos del 5% de las personas en los estudios clínicos de tratamiento combinado. Zanamivir no menoscaba la respuesta inmunológica a TIV.

Oseltamivir (tamiflu)

Las náuseas y los vómitos se informó con mayor frecuencia entre los adultos que recibieron oseltamivir para el tratamiento (náuseas, sin vómitos, aproximadamente el 10%; vómitos, aproximadamente el 9%) que entre las personas que recibieron placebo (náuseas sin vómitos, aproximadamente el 6%; vómitos, aproximadamente el 3%). Entre los niños tratados con oseltamivir, el 14% vómitos, en comparación con el 8,5% de los que recibieron placebo. En general, el 1% de la droga el tratamiento secundario a este efecto secundario, y un número limitado de adultos que se inscribieron en los ensayos clínicos de tratamiento con oseltamivir interrumpieron el tratamiento debido a estos síntomas. Similares y las tasas de eventos adversos se informaron en los estudios de oseltamivir quimioprofilaxis. Las náuseas y los vómitos pueden ser menos graves si oseltamivir se toma con alimentos. Estudios publicados no han evaluado si oseltamivir perjudica la respuesta inmunológica a TIV.

Neuropsiquiátricos eventos transitorios (auto-lesión o delirio) postcomercialización se han notificado entre las personas que tomaron oseltamivir, la mayoría de los informes se encontraban entre los adolescentes y los adultos que viven en Japón. La FDA aconseja que las personas que recibieron oseltamivir ser supervisados de cerca por el comportamiento anormal.

Uso durante el embarazo

Oseltamivir, zanamivir son “Embarazo Categoría C”, los medicamentos, lo que indica que los estudios clínicos no se han llevado a cabo para evaluar la seguridad de estos medicamentos para las mujeres embarazadas Debido a los efectos no conocidos de la gripe medicamentos antivirales en las mujeres embarazadas y sus fetos, estos fármacos deberían utilizarse durante el embarazo sólo si el beneficio potencial justifica el riesgo potencial para el embrión o feto, de los fabricantes el prospecto debe ser consultado. Sin embargo, no hubo efectos adversos se han notificado entre las mujeres que recibieron oseltamivir o zanamivir durante el embarazo o los niños nacidos de esas mujeres.

La peor pandemia de la historia de la humanidad: la gripe española.

Resumen.

En la actualidad la globalización y la facilidad para que la población mundial se comunique, no solo permite el intercambio comercial y cultural, también representa un riesgo para la salud humana, sin embargo las enfermedades infecciosas pueden ser mas poderosas que el progreso humano alcanzado en el siglo XX e incluso principios del XXI, la gripe española de 1918 representa un ejemplo del poder inimaginable que tienen esos seres microscópicos para cambiar el curso de la historia humana, en especial hoy que existe el riesgo de que esta enfermedad viral como otras bacterianas se usen como armas de destrucción masiva.

El objetivo de esta breve revisión es poner en perspectiva el alcance que tuvo la gripe española en la historia de la sociedad moderna del siglo XX y la incertidumbre en términos de la salud humana en el futuro cercano, a mediano y largo plazo, si las políticas públicas de los gobiernos del mundo, no consideran como una verdadera prioridad la prevención de enfermedades infecciosas como la gripe española.

Palabras clave. *Enfermedad, salud, virus, calidad de vida, políticas de salud mundial.*

1.- Introducción y Antecedentes.

En Octubre de 1918, el mundo al final de la I Guerra Mundial se mantenía la censura en la prensa. Un país neutral en el conflicto, España, informo que la población civil en algunas naciones del mundo había enfermado y moría rápidamente, por esta razón pasó a la historia con el nombre de gripe española; esta pandemia se cree que comenzó en dos posibles sitios en 1917 en el Tibet y se propago por las movilizaciones militares de la primera guerra Mundial, otra hipótesis señala que el 4 de marzo de 1918, entre soldados acuartelados en Kansas, E.U.A, mientras esperaban su traslado a Europa, desde ahí se extendió a Francia con la llegada de los soldados norteamericanos, tras numerosas muertes por gripe, en julio de 1918 (1-5)

Se llama epidemia al rote de una enfermedad que ataca a muchas personas en un mismo lugar, un vecindario una ciudad o todo un país. Una pandemia es una epidemia a escala mundial.

El mundo estuvo en “paz”, cuando la Primera Guerra Mundial terminó el 11 de noviembre de 1918, al mismo tiempo que la gripe española se extendía en el planeta, de los que vivieron en aquella época, pocos no enfermaron, en ese año la esperanza de vida en Estados Unidos de América (EUA)se acortó más de diez años. Según se relata en el libro la *The Great Influenze* o “ La gran gripe”,: “en Río de Janeiro, un estudiante de medicina Ciro Viera Da Cunha esperaba el tranvía cuando un hombre le preguntó algo y en el acto, murió, en Ciudad del Cabo, Sudáfrica, C Lewis subía a un tranvía para regresar a casa cuando el conductor se desplomó y murió; durante el trayecto de cinco kilómetros fallecieron seis personas mas por la misma causa (6-10).

La medicina desconocía la causa de la enfermedad y su forma de contagio, se tomaron medidas en salud pública: como la cuarentena en los puertos, se cerraron cines, iglesias y otros sitios públicos de concentración humana. En San Francisco, Cal, EUA, las autoridades ordenaron a la población usar mascarillas, quién no lo hiciese en vía publica, fue multado o encarcelado, nada fue eficaz, la gripe no discriminaba a nadie, los principales afectados por la epidemia no fueron personas de edad avanzada, sino jóvenes aparentemente sanos, la mayoría tenían entre 20 y 40 años (2-6) en el mismo país, en Filadelfia, Pensilvania en octubre de ese año, la enfermedad fue tan grave que los ataúdes no fueron suficientes, un fabricante de féretros aseguró que habría vendido 5000 en dos horas de haberlos tenido, ya que el depósito de cadáveres de la ciudad tenía diez cuerpos por cada féretro disponible (11-15). Ni las islas tropicales se libraron, en Samoa Occidental, la enfermedad llegó por barco el 7 de noviembre de 1918, en dos meses murió el 20% de sus 38,302 habitantes, no hubo ningún país del mundo sin perdidas humanas (10)
En relativamente poco tiempo, la gripe causó mas mortalidad que cualquier otra enfermedad en la historia humana, se reportaron 21,000,000 decesos en el mundo, epidemiólogos suponen que la cifra fue mayor de 50 a 100 millones (16)

La gripe española provoco más muertes en un año que la peste negra en la Edad Media en un siglo; más en veinticuatro semanas que el SIDA en veinticuatro años, más norteamericanos fallecidos que las bajas en las dos guerras mundiales. Se especula que si una enfermedad así, se disemina y contagiase a un porcentaje similar de la población humana actual en los EUA y otros países, morirían un millón y medio de personas en breve tiempo, lo que supera la mortalidad anual por enfermedades: cardíacas, cáncer, apoplejías, pulmonares crónicas, SIDA y Alzheimer. La gripe española ha sido la pandemia más devastadora de la historia de la humanidad (14-18)

2.- La medicina sin solución.
A principios de la I Guerra Mundial, la medicina logró avances en la lucha contra las enfermedades, incluso durante el conflicto bélico, los médicos habían reducido los efectos de las enfermedades infecciosas, en una publicación del *The Ladies Home Journal,* se “ afirmó que los norteamericanos ya no requerían una habitación para velar a los muertos y proponía llamar de ahí en adelante a ese sitio: “*living rooms”,* que en castellano significa “sala para vivos“.

Los médicos de 1918 fueron parte del mayor fracaso de la medicina del siglo XX, si se mide el progreso en función del número total decesos.

Los medicos captaron la magnitud de la pandemia, sabían curar las neumonías secundarias por bacterias y propusieron medidas sanitarias que habrían salvado miles de personas, pero los políticos no les escucharon.

3.-Un virus patógeno humano.
El virus causante de la gripe o influenza, es un virus que se transmite de una persona a otra por secreciones respiratorias expulsadas al toser, estornudar y hablar.

El libro Virus, pestes e historia explica:"Los italianos acuñaron el término influenza en el año 1500 para designara las enfermedades atribuidas a la 'influencia' de las estrellas, en el siglo XVIII los franceses dieron el nombre de grippe para referirse a los mismos síntomas."

Es común en el mundo, incluso en los trópicos, donde aparece en cualquier época del año, en el hemisferio norte, la temporada de gripe inicia de noviembre a marzo, en el hemisferio sur, de abril a septiembre.

El virus de la gripe de tipo A es el más patogénico es pequeño en comparación con otros en forma de esfera con proteínas que se proyectan a modo de púas, cuando infecta una célula humana, se reproduce tan rapido que, en menos de diez horas, salen a través de la membrana celular entre 100.000 y 1, 000, 000 de nuevas copias del virus, un propiedad fundamental de este agente es mutar, se reproduce, incluso en un tiempo mas corto que el VIH, sus numerosas copias no son exactas, cambian para que el sistema inmunológico no las detecte, por eso, cada año se conocen nuevas tipos de gripe con antígenos que retan y frecuentemente vencen la inmunidad humana, si el antígeno se modifica lo suficiente, el sistema de protección no se defenderá, en consecuencia habrá numerosos enfermos, para ir de una epidemia localizada a una pandemia (20)

Los virus de la gripe, o influenza, infectan a animales, es otra amenaza para la salud humana, ya que el cerdo es portador de variedades que también atacan a pollos, patos y otras especies animales, que a su vez infectan al hombre, si dos tipos de virus, animal y humano contagian al mismo cerdo, los genes de ambos virus se mezclarán y darán origen una nuevo tipo de gripe, contra la que el hombre no tiene inmunidad (21-25).

La situación de intercambio de virus sucede comúnmente en las condiciones rurales, donde conviven aves, cerdos y personas, circunstancia frecuente en Asia y en todo país del planeta, estos sitios son posibles fuentes de nuevas tipos de gripe (26-30).

Se calcula que aproximadamente cada once años surge una epidemia de influenza, cada treinta, una grave, han pasado treinta y cinco años desde la última pandemia de influenza, el intervalo más largo entre pandemias del que se tienen datos es de treinta y nueve años (25,31, en consecuencia el próximo

virus pandémico podría surgir en China o en un país cercano, es posible que incluya antígenos de su envoltura o factores de virulencia derivados de virus de gripe animal, si es así, la enfermedad se propagará rápidamente por el mundo, afectara personas de toda edad, habrá trastornos generales en las actividades sociales y económicas a escala internacional, la mortalidad será elevada, de pronostico reservado (31-35), incluso los sistemas de salud de las naciones con economía desarrolladas serán incapaces de responder a la demanda de atención médica (3,8,14,21), entonces es de suponer la situación de caos, enfermedad y daño en los países pobres (1-4).

Al comparar el impacto de las enfermedades infecciosas en el mundo, la revista *Nature* o naturaleza en el 2004 publico: "que se calcula 15,000,00 de muertes anuales en el mundo relacionadas con este tipo de problemas de salud, como es el caso del SIDA, según un informe del **ONUSIDA, un programa auspiciado por las Naciones Unidas y otros organizaciones, indican: que en los 45 países más afectados por esta enfermedad, se prevé la muerte prematura de 68,000,000 de personas desde los años 2000 al 2020, de hecho ya han muerto a más de 20,000,000 de personas en los pasados 25 años, en contraste con la gripe española que mató millones, pero en poco más de un año (36-40).**

El 19 de Mayo de 2005, el servicio de noticias para organizaciones humanitarias *Alert Net,* de la Fundación Reuters, reporto la continua aparición de nuevos virus de gripe, lque constituyen una amenaza constante de pandemias cada vez más probables, al igual que publico el diario *The Wall Street Journal: el* virus de la gripe aviar, que infecta a Asia, es el H5N1, éste se detectó por primera vez en 1997, en los mercados de aves de corral de Hong Kong el cual es capaz de causar la muerte de 80% de los animales que infecta. **Los informes de la agencias de salud, indican que podría contagiarse cualquier persona en contacto con animales enfermos, de ahí el grave riesgo para la salud publica el mundo que vive bajo presiones de insuficiente sistemas de prevención de enfermedades infecciosas, pobreza y marginación (41-43).**

4.- La clasificación del virus de la gripe española: ortomixovirus

El virus de la influenza es único miembro de la familia de los ortomixovirus, el término "mixo" se refiere a que contienen mucinas o glucoproteínas, tienen RNA de una pieza *son pequeños 110 nm, en el cuadro 1 se muestran sus principales propiedades biológicas que tienen valor diagnostico clínico.

El cuadro 2 se presenta una comparación del virus de la influenza con varios otros que infectan las vías respiratorias (1,2) que también son importantes en el mundo (14).

El virus de la influenza A, causa pandemias, el tipo B, infecciones tipo de gripe y el virus de la C solo infecciones leves de las vías respiratorias.

El virus tipo A de la influenza contiene RNA de cadena de sencilla segmentado, con una nucleocápside helicoidal y envoltura lipoproteínica, el virión contiene un RNA polimerasa (43-45). Mientras el cuadro 3 muestra las

principales propiedades de las envolturas de los paramixovirus, que se usan para su identificación clínica (5,13,37).

Cuadro 1. Propiedades biológicas de ortomixovirus y paramixovirus causantes de infecciones respiratorias en humanos.

Propiedad	Ortomixovirus	Paramixovirus
Virus	Influenza tipos A, B y C	Sarampión, paperas, sincitial respiratorio y parainfluenza
Genoma	segmentado (8 piezas), RNA de tira sencilla y polaridad Negativa	No segmentado, RNA de una tira sencilla y polaridad negativa
RNA polimerasa del virión	si	si
Cápside	helicoidal	helicoidal
Envoltura	si	si
Tamaño	menores de 110 nm	mayores de 150nm
Espiculas de superficie	hemaglutina - neuraminidasa en espigas diferentes	Hemaglutinina-neuraminidasa en la misma espiga*
Formación de células Gigantes	No	si

***Cada virus de este grupo difiere en los detalles (34,41).**

dependiente de RNA, que transcribe al genoma con una polimerasa negativa a mRNA, este genoma no es infeccioso, su envoltura está cubierta de dos tipos de espículas, una hemaglutinina y una neuraminidasa. ***** la primera aglutina eritrocitos y la última degrada al ácido muráminico, un componente químico básico de la superficie de la membrana de la célula humana (1,2,30,45).

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***** El peso molecular total del virus RNA de la influenza es de alrededor de 2-4 x 10^6, en tanto que el del paramixovirus RNA es mayor, alrededor de 5-8 x 10^6.

Cuadro No. 3 Espículas de la envoltura de los paramixovirus que infectan humanos.

Virus	Hemaglutinina	Neuraminidasa	Proteína Fusinante*
Virus del sarampión	+	-	+
Virus de la paroditis**	+	+	+
Virus sincitial respiratorio	-	-	+
Virus de la parainfluenza**	+	+	+

***Las proteínas fusionantes de sarampión y paperas son también hemolisinas.** ** En los virus de paperas y parainfluenza, hemaglutinina y neuraminidasa están en la misma espícula, y la proteína de fusión en una espícula diferente.**

Los virus de la influenza, en particular del tipo A, tiene cambios en la antigenicidad de sus proteínas aglutinina y neuraminidasa; lo que favorece su capacidad para causar pandemias, estos cambios se atribuyen al reordenamiento o recombinación de alta frecuencia de los segmentos completos del RNA de su genoma, en este proceso se intercambian segmentos completos de RNA y cada uno codifica para una sola proteína, por ejemplo, la hemaglutinina.

Los virus de la influenza tienen antígenos específicos de grupo y de tipo.

1) La ribonucleoproteína interna es el antígeno específico de grupo que distingue a los virus de la influenza A, B, y C.
2) La hemaglutinina y la neuraminidasa son antígenos específicos de tipo localizados en la superficie con distinta antigenicidad, el anticuerpo contra la hemaglutinina neutraliza la infectividad del virus y previene la enfermedad, no así el anticuerpo contra el antígeno específico del grupo que se localiza en el interior, el anticuerpo contra la neuraminidasa, no neutraliza la infectividad del virus, pero si reduce la enfermedad, quizá por medio de la disminución del número de copias de virus liberados de las células infectadas, lo que en consecuencia disminuye su propagación para futuras epidemias (23,44,46).

Existen especies animales que tienen virus de la influenza A propios, como: las aves, los cerdos y los caballos, es probable que tales virus sean el origen de los tipos antigénicos nuevos que causan epidemias en el hombre, si un virus de influenza A equino y uno humano infectan la misma célula, en las vías respiratorias de un granjero, podría ocurrir entrecruzamiento y aparecer una variante nuevo del virus A humano, portador de la hemaglutinina del virus equino.

La nomenclatura A/Filipinas/82 (H_3N_2) define de los virus de la influenza (14,45). La "A" se refiere al antígeno de grupo, lo siguiente es la localidad y el año en que el virus se aisló, H_3N_2 es la designación de los tipos de hemglutinina (H) y neuraminidasa (N), así como se definió el de virus de la gripe española de 1918 H1N1 (1-5).

4.1 Síntesis del ciclo replicativo del virus.

El virus se adhiere a una célula cuando la hemaglutinina interactúa con los receptores glucoproteínicos de la superficie de la membrana y luego entra pierde la cápside, la RNA polimerasa del virión transcribe los ocho segmentos del genoma a ocho mRNA, que se trasladan a proteínas virales en el citoplasma. Los genomas RNA de la progenie se sintetizan en el núcleo y la ribonucleoproteína helicoidal se ensambla en el citoplasma; luego, la proteína de la matriz interviene en la interacción de nucleocápside y envoltura y el virón sale de la célula, por gemación, desde la membrana celular exterior en el sitio donde hemaglutinina y neuraminidasa se han interdigitado. La neuraminidasa actúa en la liberación de viriones al hidrolizar el ácido neurominico de la superficie celular, el virus de la influenza es el único virus RNA que replica en el núcleo.

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* Los paramixovirus también tienen una hemaglutinina y una nuraminidasa, pero las dos proteínas se ubican en la misma espiga.

4.2 Transmisión y epidemiología.

El virus se transmite por aerosoles de origen respiratorio humano. La propiedad del virus de la influenza A de causar epidemias, depende de los cambios en sus antígenos hemaglutinina y neuraminidasa, estos pueden ser de dos tipos: desplazamientos antigénicos, que son alteraciones mayores basadas en el entrecruzamiento de los fragmentos del genoma, y desviaciones antigénicas, que son modificaciones menores basados en una mutación, los desplazamientos antigénicos son menos frecuentes,alrededor de cada 10 u 11 años, en tanto que las variantes menores o desviaciones aparecen virtualmente cada año. Las epidemias y pandemias por este tipo de virus, se producen cuando la antigenicidad del virus cambia lo suficiente para que la inmunidad que poseen las personas, no sea eficaz, mientras la del virus de influenza B también varía, pero no es importante, ni frecuente y si ocurre se de en los meses de invierno cuando, con la neumonía bacteriana secundaria, causa un número significativo de muertes, en especial en ancianos (1-6;20-25)

4.3 Patogénesis e inmunidad.

Cuando este virus es inhalado, su neuraminidasa degrada la capa protectora de moco que se genera en las vías respiratorias, el virus penetra a células epiteliales de esas vías tanto en la parte superior como inferior, la infección se limita básicamente a esta área, a pesar del cuadro sistémico de la enfermedad, rara vez ocurre viremia, pero si se produce necrosis de las capas superficiales del epitelio respiratorio.

La neumonía por virus de influenza es grave por el daño en el tejido, ahi se encuentran anticuerpos IgG contra el virus, de escasa protección, mientras que la IgA secretada en las vías respiratorias sí protege.

4.4 Datos clínicos.

El periodo de incubación de la influenza es de 24 a 48 h, el enfermo repentinamente tiene fiebre, mialgias, cefalea, tos, aunque vómitos y la diarrea son poco comunes, en general, la enfermedad se resuelve de manera espontánea en un lapso de 4 a 7 días, pero una neumonía por el mismo virus o bacteriana si se complica, a continuación algunos signos de la enfermedad:

El **síndrome de Reye** un señal que se caracteriza por encefalopatía y degeneración hepática, es una complicación grave, poco común en los niños, después de algunas infecciones virales, en particular influenza B y varicela, en este caso cuando el paciente ingiere aspirina administrada para reducir la fiebre en las infección, existe evidencia de que participa en una predisposición a la enfermedad.

5.- Diagnóstico de laboratorio para la detección del virus.

Aunque la mayor parte del diagnóstico de la influenza se hace en clínica, se dispone de dos métodos en el laboratorio uno: 1) el virus se multiplica en cultivos de células de exudado faríngeo e identifica por tinción con anticuerpos fluorescentes en las células infectadas, con antisueros para influenza A y B, este método que requiere varios días; la otra es mediante 2) una determinación de la elevación del título de anticuerpos de por lo menos cuatro veces, en el

suero al inicio de la enfermedad, así como 10 días después, es suficiente para diagnóstico positivo. Para medir el título se usa la prueba de bloqueo de hemaglutinación (1,5,8,10) o de fijación del complemento (FC).

5.1 Tratamiento.

La amantadita se usa en el tratamiento y prevención de la influenza A, su principal indicación es en ancianos no inmunizados, como en casas de retiro, donde la influenza es mortal, debe reconocerse que la amantadita es eficaz solo contra la influenza A no contra la B. La **rimantidina,** derivado de la amantadita, se recomienda en el tratamiento y prevención de la gripe porque tienen menos efectos colaterales (12,18,20)

5.2 Medidas de prevención.

Existen antibióticos que reducen la mortalidad por neumonías secundarias causada por bacterias, así como contra algunos virus como la influenza, además, la vacunación combate el virus, si se identifica el tipo específico, siempre y cuando la vacunación se aplique a tiempo; pero la historia de la inmunización contra la gripe humanan ha sido de fracasos, la medicina ha tenido avances desde la I Guerra Mundial, sin embargo los grupos de investigación en el mundo aún no han descubierto o desarrollado la solución definitiva contra este tipo de virus (14,19,22).

El Instituto Nacional de Investigación Médica, de Londres, afirmó:" actualmente, existen las condiciones ambientales de 1918, con un elevado flujo internacional de personas por los medios de comunicación, desnutrición en los países pobres, falta de sanidad en las zonas de guerra, una alta proporción de la población mundial de 6,500 millones vive en zonas urbanas donde los servicios de salud son insuficientes (33,40).

La pandemia de gripe del 1918 descrita en el libro : "*Flu-The Store of the Great Influenza Pandemic of 1918 and the Search for the Virus that caused It*". "La gripe: la historia de la gran pandemia de influenza de 1918 y la búsqueda de virus que la causó", señala: a esta enfermedad se le dio el nombre de gripe, aunque, nunca antes hubo otra igual; comenzó a final de la I Guerra Mundial 1914 – 1918 en la llamada "la Gran Guerra," Mientras que en la publicación *Microbes and Infection*, o microbios e infección, se explica "que existen motivos para pensar que se podría producirá otra pandemia similar", si las políticas públicas de salud no cambian diametralmente, parece inevitable que suceda. En el libro: *Emerging Infectious Diseases,* o "las enfermedades infecciosas emergentes", antes la posición de los optimistas era que para el siglo XXI, ya se habrían erradicado las enfermedades infecciosas"; sin embargo, como se ha escrito, "estas no desaparecerán mientras existe la vida como la conocemos en su diversidad" (1,13,24,37).

Por lo cual el principal modo de protección contra la gripe, es la vacuna, preparada con virus de influenza A y B muertos, la que tiene que ser formulada de cada año con los antígenos actuales, no son adecuados inmunógenos, pues solo protege por seis meses. Se recomienda un refuerzo anual, administrado antes de la estación de los resfriados, por ejemplo, en octubre, este refuerzo es la oportunidad de inmunizar contra los últimos cambios

antigénicos del virus, esta vacuna es para adultos mayores de 65 años, al igual que aquellos con enfermedades crónicas, o trastornos respiratorios y cardiovasculares, la vacuna que contiene virus muertos completos, se prepara de otras dos formas: una con fragmentos del virus y la otra con un antígeno de la superficie del virus purificado, la que se recomienda para niños porque causa menos efectos secundarios (1,23,35).

Actualmente existe una vacuna experimental eficaz, con un mutante vivo sensible a la temperatura, este virus se replica en los pasajes nasales que tienen una temperatura menor 33°C e induce la formación de la IgA, pero no en las vías respiratorias inferiores mas calientes con temperatura de 37°C, esta vacuna inmuniza sin causar enfermedad (1-6:15-20).

6.- Una esperanza para la humanidad.

En 1997 en Brevig, una aldea Inuit en la tundra de la península de Seward Alaska, un científico analizó el cadáver de una joven mujer descubierta en el en una mezcla de suelo arcilloso materia organica y hielo, que murió de gripe en 1918. El investigador aisló de los pulmones de esta mujer, el virus responsable de esa variedad de la gripe, lo analizó con técnicas genéticas, del cual recupero el ARN y descubrió la causa que hizo al virus ser tan patógeno, e identifico y secuenció genoma del virus , al igual que otro grupo de trabajo pero con muestras de pulmones de soldados fallecidos durante la I Guerra (17-25), como resultado de estos trabajos el 6 de febrero del 2005 en Science se publico un articulo por Sir J Skehel del Instituto Nacional de Investigación Médica de Londres y por el profesor Ian Wilson del Scripps Research Institute de San Diego, Ca, EUA, que obtuvieron la síntesis de la proteína hemaglutinina responsable de la epidemia de 1918, en octubre del mismo año *Science* publico la secuencia genética de ese virus H1N1 obtenido de tejido humano previamente señaladas (1,2)

7.- Conclusión.

Las enfermedades infecciosas causadas por virus representan un grave riesgo para la salud, de millones de personas que viven en zonas en el mundo donde los servicios públicos relacionados, con la prevención de enfermedades, no existen o son insuficientes lo que hace a esa población mas susceptibles al contagio, lo anterior agravado por la falta de educación para salud, en la cual las autoridades de los países sin distinción de poder económico invierten poco comparado con los presupuestos que se manejan para armas y/o guerra. Por otro lado tienen un extraordinaria facilidad genética para intercambiar o combinarse con virus ajenos a la respuesta del cuerpo humano, lo que complica la situación pues estamos en estrecha interacción con animales que son necesarios en la alimentación de la población. Es por tanto necesario modificaciones sustanciales en las políticas públicas, sistemas de salud del estado y privadas para evitar un problema como la gripe española que ponga en riesgo el futuro de la humanidad.

Influenza (Flu)

The Agent

Flu is a contagious respiratory illness that is caused by a group of continuously changing viruses called influenza viruses. Nearly everyone has experienced the fever, aches, and other symptoms of the seasonal flu outbreaks that afflict 5 – 20% of Americans each year. Although these yearly flu epidemics can be fatal in some people, such as the elderly, young children, and people with certain heath conditions, flu is generally not a life-threatening disease in healthy individuals.

However, every few decades or so, a new version of the influenza virus emerges in the human population that causes a serious global outbreak of disease called a pandemic. These pandemics cause widespread illness, death even in otherwise healthy people, social disruption, and economic loss. Several years ago, scientists and public health officials feared that we might be on the brink of a new pandemic – the so-called avian or bird flu – that began circulating among poultry, ducks, and geese in Asia and spread to Europe and Africa. To date, the avian flu virus has not acquired to ability to spread easily from person to person – a necessary step in order for a virus to cause a pandemic.

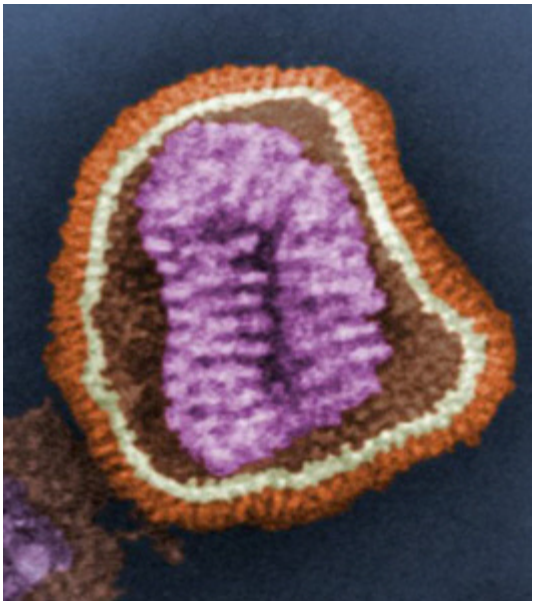
Now, a swine flu that has not been seen before has suddenly emerged that is capable of infecting humans and being transmitted from person to person. If transmission becomes sustained, this virus has the potential to cause a pandemic.

In this section, there is information on

- Different types of influenza virus
- What influenza viruses are made of
- How influenza viruses change
- Influenza epidemics and pandemics
- Avian Influenza

- Swine Influenza

Different Types of Influenza Virus



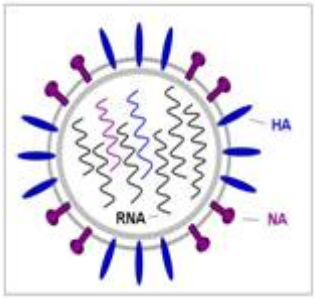
Courtesy: *CDC*
Cynthia Goldsmith, Dr. Erskine. L. Palmer; Dr. M. L. Martin

There are three different types of influenza virus – A, B, and C. Type A viruses infect humans and several types of animals, including birds, pigs, and horses. Type B influenza is normally found only in humans, and type C is mostly found in humans, but has also been found in pigs and dogs. Influenza pandemics are caused by type A viruses, and therefore these are the most feared type of influenza virus; neither types B or C have caused pandemics.

Type A influenza is further classified into subtypes depending on which versions of two different proteins are present on the surface of the virus. These proteins are called hemagglutinin (HA) and neuraminidase (NA). There are 16 different versions of HA and 9 different versions of NA. So for example, a virus with version 1 of the HA protein and version 2 of the NA protein would be called influenza A subtype H1N2 (A H1N2, for short). Although many different combinations of these two proteins are possible, viruses with only a few of the possible combinations circulate through the human population at any one time. Currently, subtypes H1N1, H1N2, and H3N2 are found in people. Other subtypes can infect animals. The subtypes that circulate through the population change over time. The H2N2 subtype, which infected people between 1957 and 1968, no longer circulates among humans. The influenza A subtypes are further classified into strains, and the names of the virus strains include the place where the strain was first found and the year of discovery.

What Influenza Viruses are Made of

Influenza virus has a rounded shape (although it can also be elongated or irregularly shaped) and has a layer of spikes on the outside. There are two different kinds of spikes and each is made of a different protein – one is the hemagglutinin (HA) protein and the other is the neuraminidase (NA) protein. The HA protein allows the virus to stick to a cell, so that it can enter into a host cell and start the infection process (all viruses need to enter cells in order to make more copies of themselves). The NA protein is needed for the virus to exit the host cell, so that the new viruses that were made inside the host cell can go on to infect more cells. Because these proteins are present on the surface of the virus, they are "visible" to the human immune system.



Inside the layer of spikes, there are eight pieces, or segments, of RNA that contain the genetic information for making new copies of the virus. Each of these segments contains the instructions to make one or more proteins of the virus. So for example, segment 4 contains the instructions to make the HA protein, and segment 6 contains the instructions to make the NA protein (the segments are numbered in size order, with 1 being the largest). When new viruses are made inside the host cell, all eight segments need to be assembled into a new virus particle, so that each virus has the complete set of instructions for making a new virus. The danger occurs when there are two different subtypes of influenza A inside the same cell, and the segments become mixed to create a new virus.

How Influenza Viruses Change

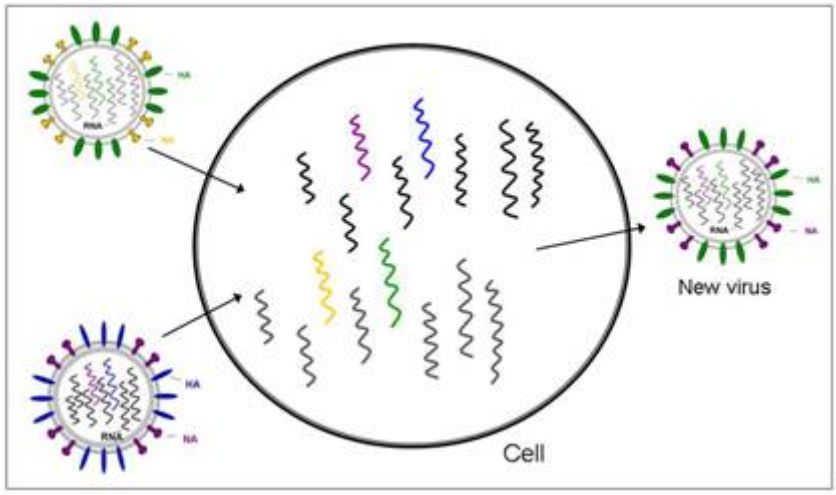
Influenza virus is one of the most changeable viruses known. There are two ways that influenza virus changes – these are called drift and shift.

Drifting, or antigenic drift, is a gradual, continuous change that occurs when the virus makes small "mistakes" when copying its genetic information. This can result in a slight difference in the HA or NA proteins. Although the changes may be small, they may be significant enough so that the human immune system will no longer recognize and defend against the altered proteins. This is why you

can repeatedly get the flu and why flu vaccines must be administered each year to combat the current circulating strains of the virus.

Shifting, or antigenic shift, is an abrupt, major change in the virus, which produces a new combination of the HA and NA proteins. These new influenza virus subtypes have not been seen in humans (or at least not for a very long time), and because they are so different from existing influenza viruses, people have very little protection against them. When this happens, and the newly created subtype can be transmitted easily from one person to another, a pandemic could occur.

Virus shift can take place when a person or animal is infected with two different subtypes of influenza. Take the case, for example, where there are two different subtypes of influenza circulating at the same time, one in humans and one in ducks. The human subtype is able to infect humans and pigs, but not ducks, while the duck subtype is able to infect ducks and pigs, but not humans. Consider what can happen when a pig becomes infected with both the human and duck influenza subtypes at the same time. Inside an infected cell, the segments of both viruses are scrambled or reassorted, so that a human virus particle is assembled that contains the duck HA segment instead of the human HA segment. A new virus subtype has been created. This new subtype can infect humans, but because it has the new duck version of the HA protein, the human immune system would not be able to defend an infected person against the new virus subtype. The virus may continue to change to allow it to spread more easily in its new host, and widespread illness and death could result.



Reassortment of the genetic material of two different influenza subtypes within an infected cell to produce a new virus subtype.

Virus shift can also occur when an avian strain becomes adapted to humans, so that the avian virus is easily transmitted from person to person. In this case, the

avian strain jumps directly from birds to humans, without mixing or reassortment of the genetic material of influenza strains from different species.

Influenza Epidemics and Pandemics

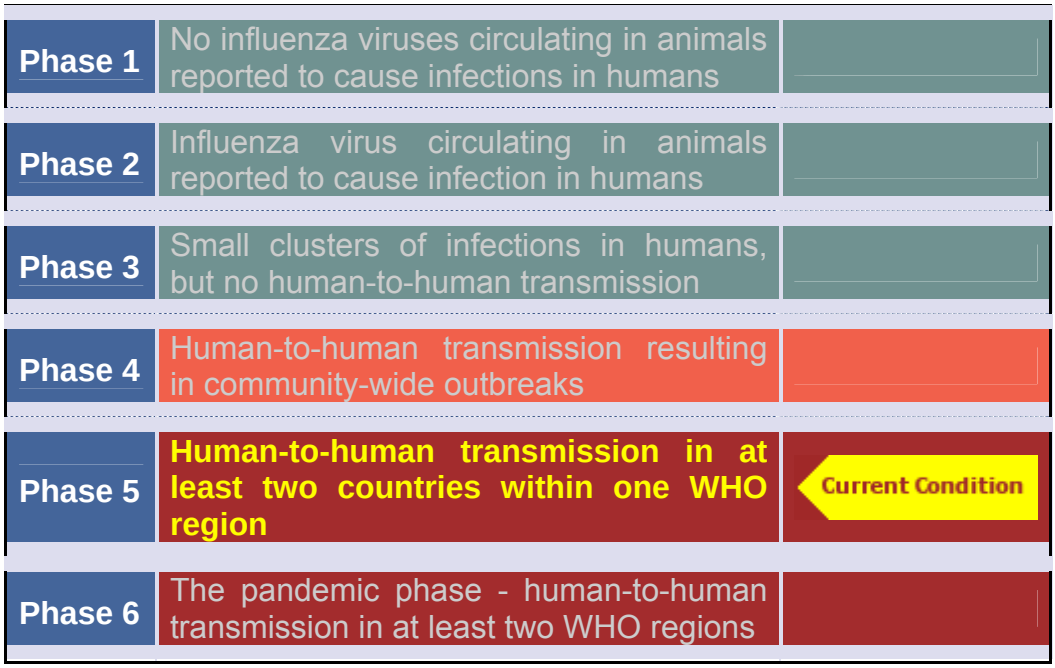
Influenza epidemics occur annually and are the most common emerging infection among humans. These epidemics have major medical impacts and are known as interpandemic epidemic influenza.

Pandemics happen every few decades. They occur when a new subtype of influenza A arises that

- has either never circulated in the human population or has not circulated for a very long time (so that most people do not have immunity against the virus).
- causes serious illness.
- can spread easily through the human population.

There were three influenza pandemics in the 20 th century – the “Spanish flu” of 1918-19, the “Asian flu” of 1957-58, and the “Hong Kong flu” of 1968-69. The 1918 flu was by far the most deadly. More than 500,000 people died in the United States as a result of the Spanish flu, and up to 50 million people may have died worldwide. Nearly half of those of those deaths were among young, otherwise healthy individuals.

The World Health Organization (WHO) has defined six phases of a pandemic.



The WHO set the alert level to Phase 3 in 1997 following reports of human infections by the H5N1 avian influenza virus. After the H1N1 swine influenza

virus emerged and was shown to be passing from person to person in Mexico, the alert level was raised to Phase 4 on April 27, 2009. Two days later, on April 29, the WHO again increased the alert level, this time to Phase 5, reflecting the sustained transmission of the new H1N1 virus in the United States. Phase 5 strongly suggests that a pandemic is imminent. If sustained human to human spread of the H1N1 influenza virus occurs in another region of the world, then the alert level would increase to the highest phase. Phase 6 would indicate that we have entered the global pandemic phase.

It is important to keep in mind, however, that the term “pandemic” indicates sustained human-to-human spread of the virus in more than one region of the world, but does not indicate the severity of disease caused by the virus. A pandemic, such as the 1918 influenza pandemic, can be very lethal, but the 2009 H1N1 virus appears to produce a much milder illness. Therefore even if the 2009 H1N1 is declared a pandemic, it could still produce a mild illness.

Avian Flu

Influenza naturally infects wild birds all around the world. Wild birds do not usually become ill from influenza, but it is very contagious and when domesticated birds, such as chickens, ducks, or turkeys become infected, they can become ill and die.

Humans do not generally become infected with avian flu. This is why news of humans contracting avian influenza during an outbreak of bird flu in poultry in 1997 in Hong Kong was alarming. It indicated that the virus had changed to allow it to directly infect humans. The virus that caused this outbreak is influenza A subtype H5N1.

Since 1997, H5N1 infections in birds have spread. H5N1 initially spread in birds throughout Asia. Wild birds have since brought H5N1 to countries along their migratory routes – first Russia and eastern Europe and then to countries in western Europe. H5N1 infections in birds have now been reported in most countries of Europe including the United Kingdom, Spain, Greece, Italy, Germany, and France. H5N1 has also been detected in Turkey, Iraq, Iran, Pakistan, and India and in countries on the African continent, including Egypt, Sudan, and Nigeria.

The number of cases of avian flu worldwide has topped 400 and there have been close to 250 deaths. It is possible, however, that additional infections have occurred that were unreported or unconfirmed or did not produce symptoms of infection, so the actual death rate may be lower. Most human cases have been traced to direct contact with infected poultry, but there have been a few cases where person-to-person transmission is suspected, particularly in clusters

where multiple family members became infected. In June 2006, the first case of human-to-human transmission was confirmed by the WHO. This event occurred within a family in Indonesia. Another case of H5N1 transmission between two family members - this time in Pakistan - was confirmed by the WHO at the end of 2007. So far, infections in humans have not spread beyond persons with close, prolonged contact with an infected individual.

Courtesy:CDC
Taronna Maines and Greg Knobloch

Scientists have recently discovered one reason why avian H5N1 is not readily transmissible among people. As with other viruses, the influenza virus must attach to specific proteins called receptors on the outside of cells in order to gain entry into cells and cause an infection. It is the hemagglutinin or HA protein of the influenza virus that determines which cell type the virus can enter. Unlike human influenza viruses which infect cells high in the respiratory tract, the H5N1 HA protein attaches to cells much lower in the respiratory track. The virus is so deep within the respiratory tract that it is not coughed up or sneezed out, and so it does not easily infect other people. If the HA protein of H5N1 were to mutate so that it could infect cells higher in the respiratory tract, then it would more likely be able to pass from person to person.

In addition to H5N1, other avian influenza strains have occasionally infected humans in recent years. These include the H7N2 strain which infected two individuals in the eastern United States in 2002 and 2003, and the H9N2 strain which has caused illness in several people in Asia in 1999 and 2003. However, H5N1 is currently the greatest concern because of its rapid mutation rate, geographic spread, and ability to cause severe illness in humans. However, in the time since the H5N1 virus first emerged, it has not acquired the ability to spread easily within the human population, and so concern that this virus could cause the next pandemic has lessened.

Swine Flu

Swine influenza, or swine flu, is a very contagious respiratory disease of pigs. Swine flu viruses produce high levels of illness in pigs, but do not generally

cause them to die. Pigs may become infected year round, although the highest incidence of infection occurs in late fall and winter, similar to outbreaks in humans. In addition to infection with swine influenza viruses, pigs are also susceptible to infection by avian influenza or human seasonal influenza viruses. This can lead to mixing of the different influenza types, causing reassortment, resulting in the creation of new virus subtypes.

Swine influenza viruses do not usually infect humans, except for occasional cases where a person has had close contact with an infected pig. In 1976, a highly publicized outbreak of swine flu occurred among soldiers in Fort Dix, New Jersey. The cause of this outbreak was a swine influenza virus that mutated in such a way to allow it to spread among humans. This virus caused disease and one death among otherwise healthy individuals. There was limited transmission outside of the group from this facility, and the virus disappeared after a short time.

In the past few weeks, a new influenza virus has emerged that is capable of infecting humans and spreading from person to person. This virus is called influenza A H1N1, although is commonly referred to as swine flu. It is distinct from the swine flu virus of 1976 and also from seasonal human H1N1 influenza viruses. Although it is called a swine flu, the new H1N1 virus is transmitted from person to person, and not through contact with pigs or pork products.

The new H1N1 virus appears to be made up of a novel combination of segments from four different influenza virus strains - a Eurasian swine virus, a North American swine virus, and avian and human influenza virus segments. Reassortment of segments from these different viruses has produced a unique virus that has not been seen before by the human population. Therefore everyone is susceptible to the newly circulating H1N1 virus, as limited or no natural immunity exists to this virus.

The epicenter of this outbreak appears to be Mexico with over 500 confirmed cases. There are currently over 220 confirmed cases in the United States with the greatest number of cases in New York, California, and Texas. Smaller numbers of cases have been confirmed in close to ten European countries and in countries around the world including Israel, New Zealand, Hong Kong, Costa Rica, and Columbia. The number of laboratory confirmed cases in the United States and worldwide is increasing on a daily basis, and additional cases are suspected. There are signs, however, that the outbreak may have peaked in Mexico, the first country to report H1N1 infections.

In the United States and most other countries, the 2009 H1N1 virus has produced relatively mild illnesses. There has only been one death reported in the United States of a Mexican toddler who received treatment in Texas. The 2009 H1N1 virus does not appear to possess the genetic signature of highly

lethal flu strains. However, experts caution that deaths from the new H1N1 virus may still occur, because even the seasonal flu causes many deaths each season, primarily in the very young and the elderly.

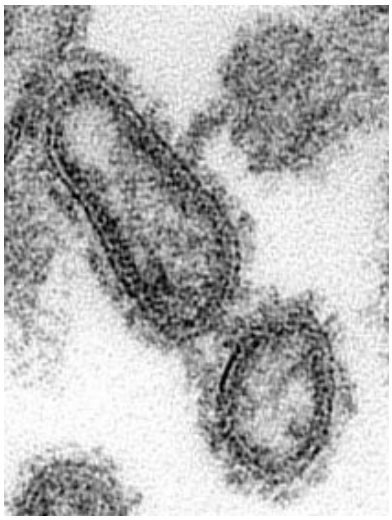
The situation in Mexico appears to be different and is puzzling. More than 100 deaths are suspected to have been caused by the H1N1 flu virus in Mexico. Unlike seasonal flu, the deaths in Mexico have occurred in young and otherwise healthy adults. One possibility is that patients delayed seeking treatment until symptoms were very severe. It is too soon to know what the mortality rate of the new H1N1 flu will be.

The H1N1 flu viruses isolated from the recent human cases are sensitive to two of the antiviral drugs used to treat influenza – oseltamivir (Tamiflu®) and zanamivir (Relenza®). Both of these drugs act by inhibiting the essential influenza neuraminidase protein. In response to the threat of a possible H5N1 bird flu pandemic, many countries have acquired stockpiles of these drugs.

Currently there is no vaccine for this virus, but the process to generate a vaccine has been initiated.

The Problem

Many experts believe that the world is currently closer to the next influenza pandemic than at any time since 1968 when the last pandemic occurred. There is concern that the 2009 H1N1 influenza virus causing the current outbreaks in the United States, Mexico, Canada, and countries in Europe and as far away as New Zealand could cause the next pandemic. It has spread to too many geographic locations too quickly to be effectively contained. The United States has declared a “public health emergency”, and the WHO has raised the alert level for pandemic risk two times over the course of three days from Phase 3 to Phase 5. This is a strong signal that a pandemic is likely to occur in the very near future.



Courtesy:CDC
C.S. Goldsmith, and T. Tumpey

The 2009 H1N1 virus appears to be a mild influenza strain causing illness similar to that seen with seasonal flu. However, influenza viruses are extremely unpredictable, and it is possible that the H1N1 virus could become more virulent over time. The flu strain that caused the 1918 pandemic was mild in the spring, but returned in a more lethal form in the fall and winter to infect about one-third of the world's population and kill an estimated 50 million people. Experts cannot predict at this time whether the new virus will remain a mild flu strain or become more dangerous with time. Therefore, it is crucial to maintain vigilance and take steps to limit the spread of the virus.

There are four different antiviral drugs, of two different classes, that are effective against influenza. However, influenza viruses can develop resistance to these drugs, so that the drugs can no longer be used to treat or prevent infections. The H1N1 swine influenza virus is sensitive to the two neuraminidase inhibitor drugs known as Tamiflu® and Relenza®, but it is resistant to the second class of drugs, the adamantanes. It would be a grave concern if the virus acquired further drug resistance.

There is no vaccine currently available to protect humans from the H1N1 swine influenza virus. The seasonal flu vaccine is not effective against the H1N1 virus because the viruses are too different.

Historically, influenza pandemics occur about three to four times each century. Experts believe that another influenza pandemic is inevitable, and even overdue. Scientists now believe that the next pandemic - as a result of the rapid geographic spread of the H1N1 swine flu - is imminent. It is too soon to know how much longer the H1N1 virus will continue to spread or how severe an illness it will cause.

The Research

Investigators in the Department of Molecular Virology and Microbiology (MVM) at Baylor College of Medicine have been studying influenza for many years with an Influenza Research Center first being established in 1974. A major focus of their effort is currently directed towards the development and testing of influenza vaccines to find the most effective vaccination dosages, methods, and strategies to protect the population against this deadly disease. They are well prepared and ready to begin testing vaccines against the 2009 H1N1 (swine) influenza virus as soon as they become available. Research is currently being conducted by MVM investigators on

- Epidemic influenza which occurs annually and is attributable to minor changes in genes that encode proteins on the surface of circulating influenza viruses. These are known as interpandemic epidemics.
- Pandemic influenza [link to research section below] which occurs when more significant changes in the influenza A virus arise when human virus strains acquire genes from influenza viruses of other animal species. When this happens, everyone in the world is susceptible to the new virus, and a worldwide epidemic - or pandemic - can result.
- H1N1 (swine) influenza, a new flu virus that emerged in the spring of this year, which appears to be on the brink of causing a pandemic.

Epidemic Influenza

Courtesy:CDC

MVM investigators would like to better understand interpandemic influenza infections, disease, and vaccines with the goal of developing ways to better control these epidemics. Towards this goal, they are working on developing new improved vaccines against epidemic influenza strains and are trying to understand how the immune systems of different people respond to the influenza virus and influenza vaccines.

The following research projects are ongoing.

- Developing new vaccines for induction of humoral and cell-mediated immune responses against influenza viruses that can prevent or modify infections.
- Identifying the optimal way to induce mucosal immune responses to influenza viruses that can increase resistance to infection at the site where infection initially occurs.

- Searching human genes for single nucleotide polymorphisms that determine the pattern and magnitude of immune response to influenza virus or provide an explanation for illness and its severity.
- Determining the role of immune responses directed toward the different proteins of influenza, including new candidates, for a beneficial role.
- Performing clinical trials of new and experimental vaccines as part of a program for development of improved influenza vaccines.
- Developing improved methods for measuring immune function in humans.

MVM researchers are also conducting a study (in collaboration with Kelsey-Seybold Clinics) to monitor the safety of inactivated influenza vaccine administered to pregnant women. They want to determine the effectiveness of the vaccine in protecting the women that are pregnant and whether these immunized women can pass on immunity against influenza, so that their infants would be protected from influenza during their first few months of life.

Another approach that is being used by MVM researchers to protect against influenza epidemics is called herd immunity. The idea is to vaccinate a large percentage of school-age children to limit the spread of influenza without needing to vaccinate a larger percentage of the general population. The reasoning behind this idea is that school-age children are often the source of infection and pass the virus onto their friends, teachers, and family members. So preventing children from spreading influenza through large-scale vaccination of this group should protect the rest of the "herd" from influenza infection, even those who haven't been vaccinated. This might be especially helpful to the elderly population who are at higher risk from influenza-related complications and whose immune systems may not mount as effective a response to influenza as younger individuals. Another advantage to this approach is that it might be possible to achieve high community protection from influenza with a limiting amount of vaccine.

Courtesy: CDC/ James Gathany

Dr. Pedro (Tony) Piedra and colleagues are in the process of testing herd immunization in school-aged children in central Texas. In their initial study, they found that vaccination of 12 to 15% of children in selected communities resulted in an indirect protection to influenza infection in 8 to 18% of the adults in these communities. They are currently conducting a larger, school-based vaccination program with the goal of immunizing 50% of the children, and they will determine how effective this level of immunization is in preventing infection in adults. Dr. Piedra and co-workers want to know how many children need to be vaccinated in order to protect the adult population from influenza infection, and they would like to use this approach to control the spread of epidemic influenza. They also hope to use this approach as a model for combating pandemic influenza and bioterrorism.

Pandemic Influenza

The most effective way to prevent the widespread infection and high mortality rate that a new influenza virus could inflict upon the human population would be to vaccinate people, so that the human immune system would be prepared to fight off an infection. MVM investigators are trying to identify the best way to prime the human immune system to defend against avian flu strains that could cause a pandemic. They are currently testing vaccines against H5N1 and other potential pandemic flu strains and are analyzing the immune responses of different people to the vaccines.

Specific projects that are currently underway or planned for the near future include the following.

- Studies of vaccines against different potential pandemic influenza virus strains (H5N1, H9N2, and others)
- Studies of pandemic influenza vaccines given by different routes (intramuscularly, intradermally) and in different dosages
- Studies to determine whether immune responses are improved when a pandemic influenza virus vaccine strain is combined with an adjuvant
- Studies of pandemic influenza vaccines in different age groups
- Developing methods for measuring immune responses to these vaccines

The researchers in MVM conducting these studies - Drs. Robert Atmar , Robert Couch, Paul Glezen , Wendy Keitel , Innocent Mbawuike , Flor Munoz , and Pedro (Tony) Piedra - hope the results of these studies will identify the optimal and most effective dosages of vaccine to protect the public from a possible influenza pandemic.

In a separate study, Dr. B.V. Venkataram Prasad and Zach Bornholdt, a graduate student in his laboratory, have determined the structure of a region of an important influenza protein called NS1. Their work may explain, in part, why the H5N1 virus causes such a severe and often fatal illness. NS1, a protein essential for influenza infection, antagonizes the cellular immune response and is thought to play a role in virulence. The lethal H5N1 strain has a different version of the NS1 protein than the NS1 protein of other strains of influenza. By knowing the structure of the NS1 protein, these investigators can surmise how variations in the H5N1 version of NS1 may alter its ability to interact with other molecules. They hypothesize that the mutations or changes in the H5N1 NS1 protein allow it to overcome the cellular immune response more effectively than the NS1 proteins of other strains of influenza. With detailed knowledge of the structure of the NS1 protein and how it interacts with other components of the cell, it will be easier to design drugs to specifically block these interactions and possibly disrupt the ability of the NS1 protein to interfere with the host's protective immune response.

Dr. Andrew Rice and colleagues are studying an avian influenza virus protein called NS1 that has recently been shown to be associated with virulence. Proteins like NS1 that are involved in pathogenesis are important targets for novel antiviral therapeutics. The goal of this project is to identify cellular proteins that interact with NS1 and play a role in the pathogenesis of avian influenza virus infection. A critical feature of the avian NS1 protein is the presence of a protein domain at one end of the protein - the carboxyl terminus – that is termed the PDZ-ligand domain. This domain is predicted to associate with a class of cellular proteins - termed PDZ proteins - that are typically involved in cell-cell contact, cellular migration, and signaling pathways. It is notable that the NS1 protein of the virulent influenza viruses, such as H5N1, contains the PDZ-ligand domain, while other less virulent influenza viruses lack this region. Dr. Rice and colleagues have identified a number of cellular targets of the NS1 PDZ-ligand domain. Their current research involves the investigation of signaling pathways that are affected by the interaction of NS1 with specific cellular PDZ proteins and how these pathways influence viral replication and pathogenesis. A long-term goal of this project is to derive small molecules that can inhibit the interaction between the NS1 protein and its cellular PDZ protein targets, as such small molecules may be the basis for the development of novel therapeutics to treat avian influenza virus infection.

H1N1 (swine) Influenza

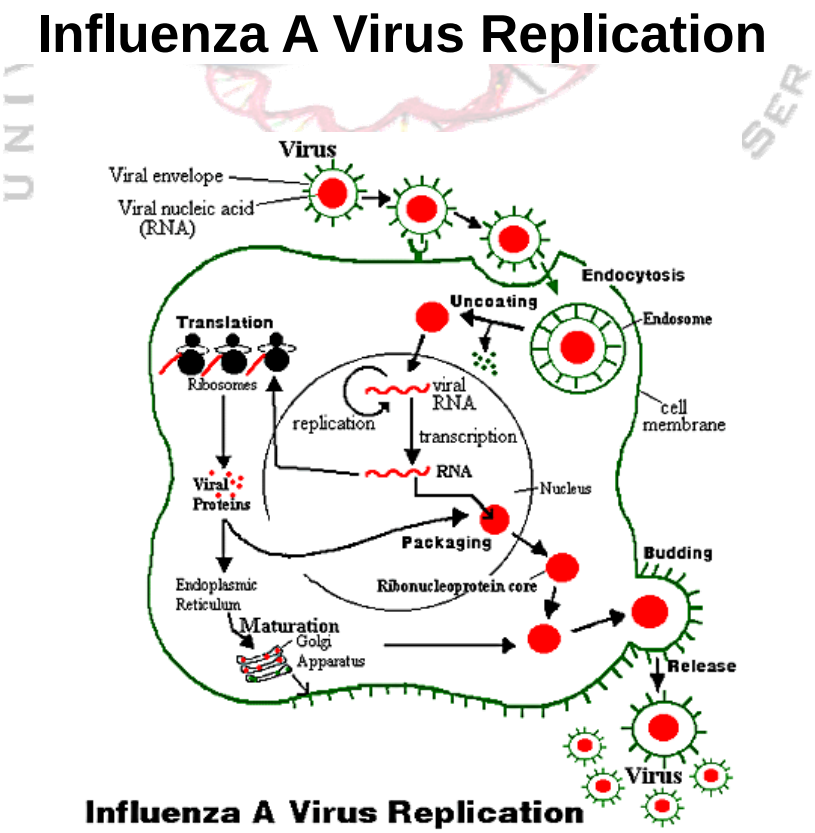
MVM researchers are actively engaged in assessing the current outbreak of the 2009 H1N1 virus and studying the virus. In addition to keeping the public informed about the outbreak through local and national media outlets, members of the Department are working on optimizing ways of collecting samples and

testing for infection, analyzing immune responses, and gearing up to do epidemiological, pathogenesis, and treatment studies of the virus.

The Vaccine and Treatment Evaluation Unit/Vaccine Research Center will be involved in several projects. In a study headed by Dr. Wendy Keitel, scientists are developing a method to collect samples and isolate viruses from suspected and confirmed cases of 2009 H1N1, so that they can assess the viruses and the innate and adaptive immune responses against them. Another study will evaluate the safety and immunogenicity of seasonal influenza vaccine in pregnant women in anticipation of the need to test novel vaccines in pregnant women.

MVM researchers are also preparing assays that will be used to detect the virus and evaluate immune responses. Dr. Pedro Piedra is working on setting up a test to detect the virus using the polymerase chain reaction (PCR). Dr. Robert Couch is setting up serologic assays for evaluation of immune responses.

As so much is currently unknown about the 2009 H1N1 virus, this work will yield valuable information to help guide public health officials in determining the best course of action in dealing with, and hopefully minimizing the consequences of, this viral outbreak.



Legend:

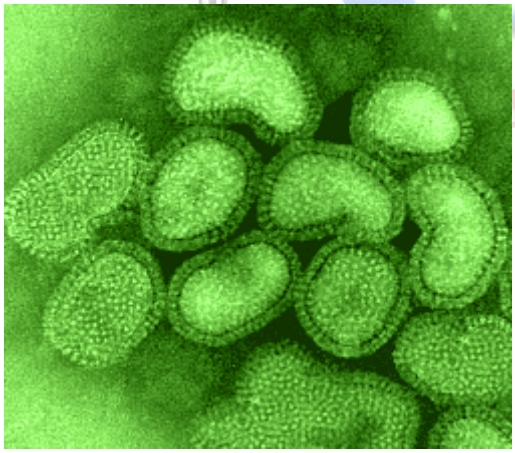
Process by which a virus enters a host cell and infects it by reproducing its own genetic material and assembling into virus particles.

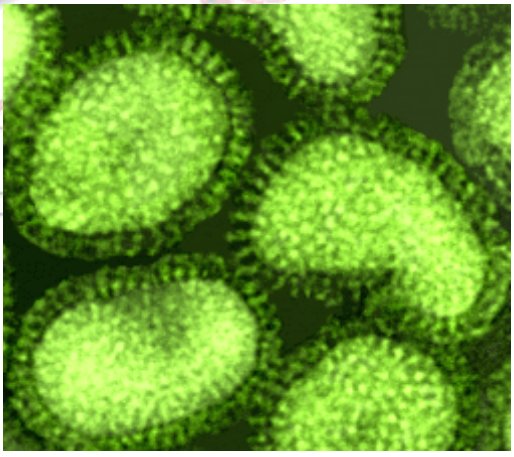
The influenza virus is a class of viruses containing RNA as its hereditary material.
It replicates by entering a host cell and using this cell's resources to produce hundreds of copies of the viral RNA.

The virus attaches to the outside of the host cell and its RNA enters into the cell. The viral genes are transcribed and translated by the cell's enzymes and ribosomes. In this way, the virus takes over the cell's productivity. Now, instead of producing only new cellular material, the cell produces hundreds of new virus particles. The new virus particles are eventually released from the cell and drift off, and some may land on a host cell of their own to pirate.

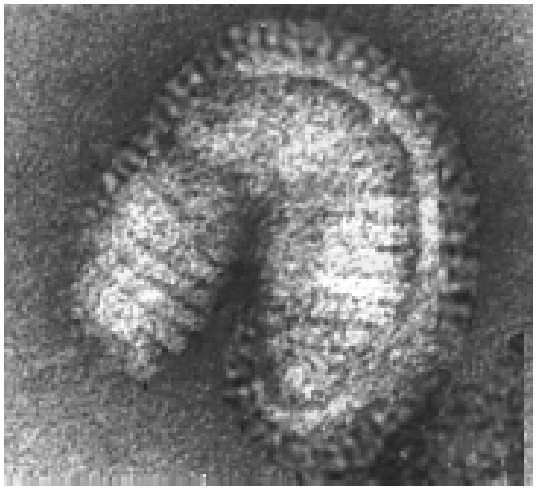
Influenza virus

Influenza virus (an Orthomyxovirus) is responsible for acute upper respiratory disease, usually accompanied by fever and myalgia.





Virions are usually roughly spherical and about 200nm in diameter.
The envelope contains rigid "spikes" of **haemagglutinin** and **neuraminidase** which form a characteristic halo of projections around negatively stained virus particles. .



The viral genome is composed of eight segments of ssRNA.
The **helical ribonucleo-protein** is not often seen,
but occasional particles show evidence of internal helical components.

The Influenza Virus Enigma

Both seasonal and pandemic influenza continue to challenge both scientists and clinicians. Drugresistant H1N1 influenza viruses have dominated the 2009 flu season, and the H5N1 avian influenza virus continues to kill both people and poultry in Eurasia. Here, we discuss the pathogenesis and transmissibility of influenza viruses and we emphasize the need to find better predictors of both seasonal and potentially pandemic influenza.

Introduction

Influenza is historically an ancient disease that causes annual epidemics and, at irregular intervals, pandemics. Seasonal influenza kills 36,000 persons annually in the United States. The impact of seasonal influenza caused by a virus showing antigenic variation in the major viral glycoproteins hemagglutinin (H) and neuraminidase (N) can be moderated by antigenically matched vaccines and anti-influenza drugs. The consequences of continuing genetic variation in seasonal influenza viruses are apparent in the current and prior influenza seasons. Despite intensive global surveillance, the H3N2 vaccine in the 2007–2008 season imperfectly matched the virus that emerged between vaccine selection and its use (6 months). In the current influenza season, the H1N1 virus that has become dominant is resistant to the anti-influenza drug oseltamivir (Tamiflu).

Pandemics that occur at irregular intervals can vary in severity from mild to catastrophic. The pandemics of the past century include the catastrophic H1N1 Spanish influenza of 1918 (more than 50 million deaths globally), the H2N2 Asian flu of 1957 (more than 1 million deaths globally), and the H3N2 Hong

Kong flu of 1968 (~0.5 million deaths globally). The natural reservoirs of these influenza A viruses are aquatic birds, and the spread of influenza to humans occurs either by direct transmission (Spanish influenza) or by reassortment between the segmented RNA genomes of avian and human influenza viruses (the Asian and Hong Kong pandemics). Although we know the general mechanisms by which new influenza viruses emerge, our basic knowledge of how these viruses acquire human pandemic potential is minimal, and our molecular understanding of the virus and the host factors involved in successful transmission and spread is rudimentary.

A highly pathogenic H5N1 avian influenza virus has been circulating for more than a decade in Eurasia and has spread to more than 60 countries. It has infected 394 humans killing 248, with recent deaths reported in China, Indonesia, Vietnam, and Egypt. The occasional direct transmission of the virus to humans and its lethality suggest the possibility of a pandemic akin to the 1918 Spanish flu if consistent human-to-human transmission is achieved. We argue that it is premature to become complacent, and we identify research directions in influenza virus ecology and the molecular biology of pathogenesis and transmission that should enable the development of better predictors of seasonal and pandemic influenza and increased preparedness (Figure 1).

Reservoirs and Surveillance

The 16 hemagglutinin and 9 neuraminidase subtypes of influenza A virus are perpetuated in aquatic birds, in which they cause no apparent disease (Peiris et al., 2007). Only viruses of the H5 and H7 hemagglutinin subtypes can become highly pathogenic after transmission to alternative hosts. Each of the H5 and H7 lineages that are lethal to domestic poultry originated from nonpathogenic precursor viruses of Eurasian and American lineages (Alexander, 2007). However, until 1996, highly pathogenic H5 and H7 viruses either were eradicated or failed to persist in nature. Today, it is unknown whether the ecology of these viruses has changed and whether highly pathogenic H5N1 viruses continue to be propagated in domestic or wild bird reservoirs. The continued circulation of Asian H5N1 viruses of multiple clades (at least 10 different clades) and subclades is unprecedented.

The available evidence suggests that all of the pandemic influenza virus strains, including the Spanish 1918 (H1N1), Asian 1957 (H2N2), and Hong Kong 1968 (H3N2) viruses, originated from the avian influenza reservoir either by reassortment (swapping of viral genetic information in hosts coinfected with more than one influenza virus) or direct transfer (Kobasa et al., 2004). Influenza outbreaks in domestic animals, including poultry, also originate from the avian reservoir. Our knowledge of the precursors of pandemic and panzootic influenza viruses is extremely limited. The available information indicates that viruses in their natural reservoirs undergo limited evolution, replicate primarily in the intestinal and respiratory tracts, and change their predominant subtypes every 2 years (Fouchier et al., 2003). Knowledge of the genomics of influenza viruses in this natural reservoir is fragmentary, and evidence suggests that there is continuing reassortment in nature (Dugan et al., 2008; Obenauer et al., 2006).

Analysis of the multiple lineages of highly pathogenic H5N1 viruses supports the contention that all of them arose in Southeast Asia (Kilpatrick et al., 2006; Smith et al., 2006). For example, the H5N1 virus that emerged at Qinghai Lake, China spread (probably in wild birds) to Europe, Africa, and India (Li et al., 2004). Similarly, the lineage that spread to Indonesia can be traced to China's Hunan Province (Wang et al., 2008). The domestic duck may be the "Trojan horse" of the H5N1 viruses, for many ducks show no signs of disease yet shed virus for up to 17 days after infection and propagate influenza virus antigenic variants with low pathogenicity (Hulse et al., 2005). This hypothesis will be resolved only by detailed molecular epidemiological studies.

To date, there is no influenza surveillance system in lower animals and birds that is comparable to the well-organized, interactive Global Influenza Surveillance Network (GISN) for human influenza. The pandemic threat of H5N1 influenza has resulted in closer collaborations between international agricultural and human health organizations. However, the lack of a counterpart of GISN at the human-animal interface is a serious shortfall in pandemic preparedness. A genomic library of all subtypes of influenza viruses in wild and domestic birds, continuously updated by high-throughput sequencing and analysis, is badly needed to identify predictors of pandemics.

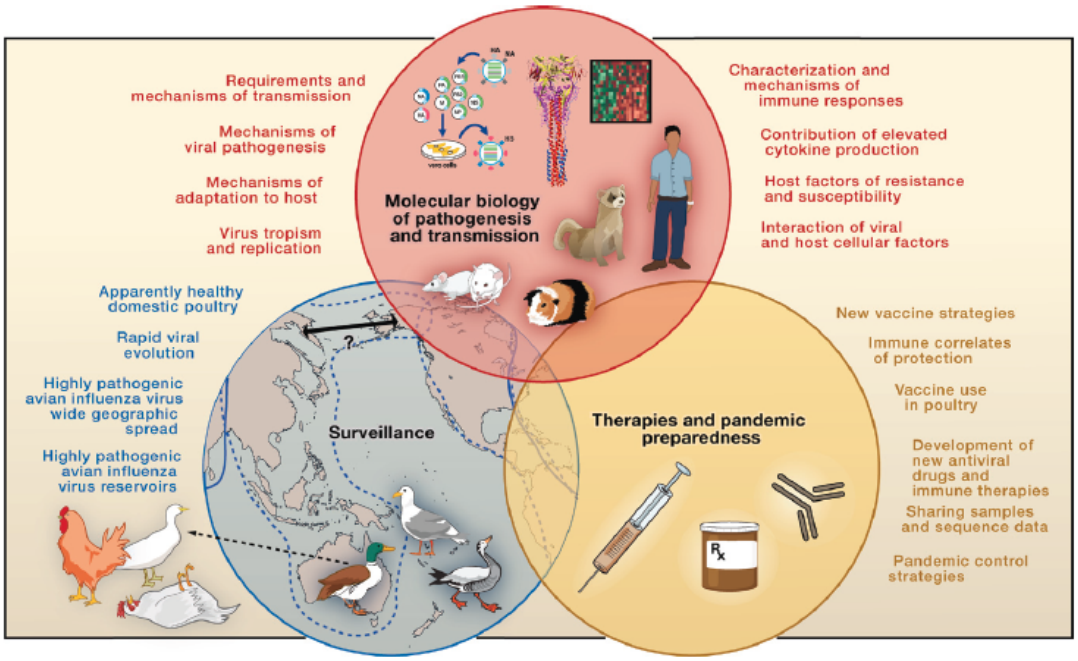


Figure 1. Spheres of Progress in Influenza Research
Shown are the three major areas of influenza research: (1) the molecular basis of pathogenicity and transmission, (2) surveillance, and (3) therapies and pandemic preparedness. Points of overlap among the three circles illustrate how the findings in each area have implications for the other two areas. The major challenges within each area of research are noted around the periphery of that circle.

Host Range and Transmission

Influenza viruses probably undergo genetic changes to spread from the wild bird reservoir to other hosts. Such changes are facilitated when multiple species of birds and mammals are housed in close proximity in live animal markets (Webster, 2004). It is unclear whether influenza viruses are transmitted directly from natural reservoirs to mammals, including humans. Notably, chickens are not susceptible to most of the low-pathogenicity subtypes, including

nonpathogenic H5 and H7 strains, without adaptation (Swayne, 2007). The involvement of intermediate hosts, including the quail and the pig, has been suggested (Matrosovich et al., 1999), but there is no smoking gun. A suggested transmission scenario might follow this sequence: wild waterfowl → domestic waterfowl → quail/pig → chicken → human. All of these birds and some mammals are found in various live markets. Information about the molecular profiles that permit transmission between these species is emerging (Perez et al., 2003), but there is much still to learn. Expansion of the host range of the Asian H5N1 avian influenza virus to felines, viverrids, stone martens, and dogs has been associated with high pathogenicity and systemic spread (Rimmelzwaan et al., 2006; Songserm et al., 2006). Extension of the host range to felid species remains to be elucidated at the molecular level; if domestic cats can serve as intermediate hosts, their infection would promote the selection of variants transmissible to humans.

The pig may be an intermediate host for interspecies spread; the replication of all avian viruses in pigs supports this notion, as does the presence of avian-type and mammalian-type virus receptors in pigs (Ludwig et al., 1995). The periodic transmission of avian influenza viruses to pigs in the absence of disease and the spread of human H1N1 and H3N2 viruses to pigs (Ma et al., 2007) are also consistent with the “mixing-vessel” hypothesis, but to date the pig has not been directly implicated in the generation of pandemic influenza viruses.

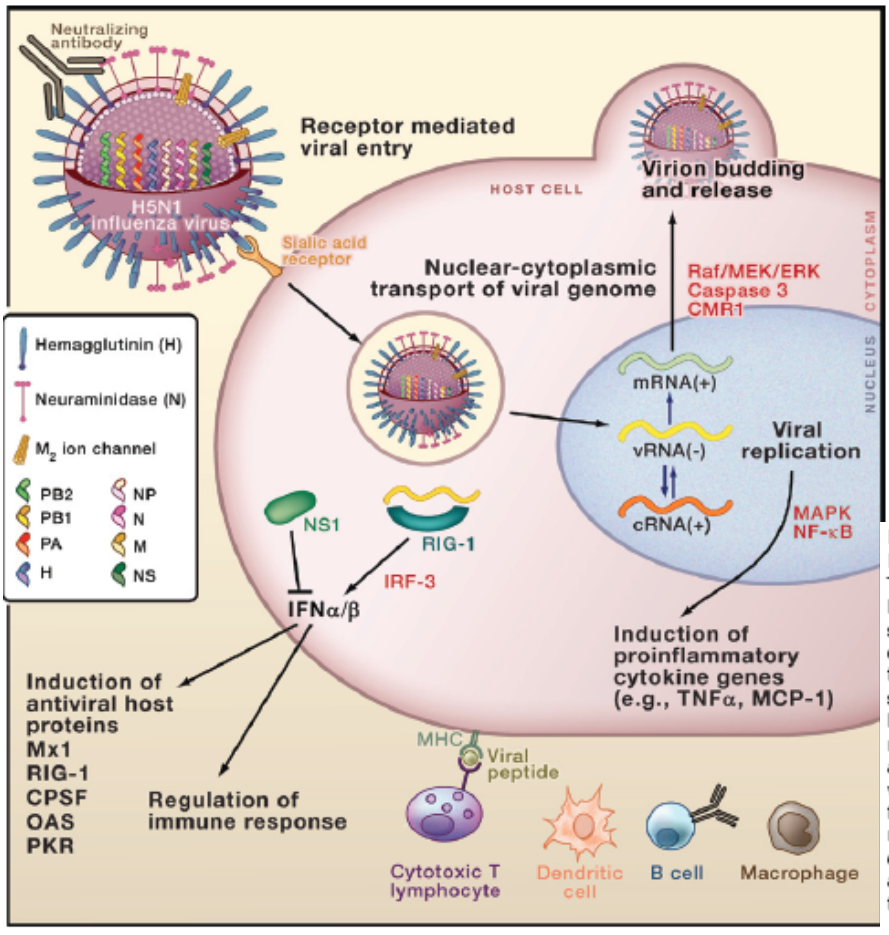


Figure 2. Molecular Basis of Influenza Pathogenesis

The life cycle of the influenza virus begins with binding of the virus to sialic acid receptors on the surface of the host cell via the viral surface glycoprotein hemagglutinin (H). This step contributes to pathogenesis, transmission, and host range restriction. Replication of the eight negative-strand RNA segments that comprise the influenza genome is central to viral pathogenesis and could be a potential therapeutic target. The release of the virion from the host cell is a hallmark of successful completion of the influenza virus life cycle. Key molecular proteins and pathways that are activated during influenza virus infection of the host cell are also depicted. Potential host signal transduction factors are indicated in red.

Viral Factors in Pathogenesis and Transmission

Receptor Specificity

A major enigma of influenza virus is whether alteration of viral specificity for host cell receptors (sialic acids) can generate a pandemic strain of virus. The viral hemagglutinin surface glycoprotein preferentially binds to certain sialic acid residues on host cells, making hemagglutinin a determinant of host range. Specific amino acid changes in hemagglutinin have been identified as important in sialic acid receptor specificity and pathogenicity (Matrosovich et al., 1999; Stevens et al., 2006b; Yamada et al., 2006). The hemagglutinin of human influenza virus isolates typically binds preferentially to α2,6-linked sialic acids, whereas that of avian influenza virus isolates has a higher affinity for α2,3-linked sialic acids (Ito, 2000). Interestingly, sialic acid receptors are distributed differently in the respiratory tracts of humans and other host species (Matrosovich et al., 2004; Shinya et al., 2006; van Riel et al., 2007). The human and ferret upper respiratory tract, believed to be the primary site of influenza infection, carries primarily α2,6-linked sialic acids, which gives human viral isolates a binding advantage. Receptor specificity must be studied at the level of the cell type to discern the relative susceptibility of cells to infection on the basis of sialic acid expression. This information will be of particular interest, as some H5N1 viruses cause systemic infection, including infection of brain cells.

Notably, the 1918, 1957, and 1968 pandemic strains all preferentially bind to α2,6-linked sialic acids (Stevens et al., 2006a), and so preferential affinity for these receptors may be necessary for emergence of a pandemic strain carrying an avian-derived hemagglutinin gene. However, avian isolates that bind preferentially to α2,3-linked sialic acids are lethal in humans and mammals and replicate well in the upper respiratory tract. Thus, it remains an open question whether H5N1 viruses must acquire specificity for binding to α2,6-linked sialic acids to become pandemic. Interestingly, cultured human respiratory epithelial cells lacking α2,3-linked sialic acids could be infected ex vivo with H5N1 viruses (Nicholls et al., 2007). This finding together with advances in glycan array technology (Stevens et al., 2006a) suggest that receptor specificity may involve factors other than binding to α2,3-linked and α2,6-linked sialic acids. However, the biological relevance of receptor binding particularly for viral entry, replication, spread, tissue tropism, and transmission still needs to be determined.

Replication Efficiency

What other viral factors increase the virulence or transmission of influenza virus, and by what mechanism? Certain H5N1 viruses with a hemagglutinin that preferentially binds to α2,3- linked sialic acids replicate in humans and can be lethal, suggesting that genes other than that encoding hemagglutinin are crucial for virulence. The replication efficiency of influenza virus correlates with its virulence. Specific amino acid sequences encoded by the polymerase genes alone are sufficient to make a virus lethal in animal models (Gabriel et al., 2005; Hatta et al., 2001; Salomon et al., 2006). The best-described marker of pathogenicity is lysine at position 627 of polymerase subunit protein PB2 (Hatta et al., 2001; Subbarao et al., 1993). This residue enhances the growth efficiency of avian H5N1 viruses in the upper and lower respiratory tracts of mice. As the importance of specific polymerase residues to lethality is identified, it will be

crucial to elucidate the mechanism by which these residues affect replication efficiency. Each of the eight negative-sense RNA segments of influenza virus is transcribed into mRNA by the viral ribonucleoprotein (RNP) complex comprised of the PB2, PB1, PA, and NP proteins (Figure 2). Crystal structures of portions of the RNP complex have already shed light on how these proteins work (He et al., 2008; Noda et al., 2006). However, more biochemical research into the structure of the complex is needed to reveal why certain residues affect the interaction of the polymerase proteins, viral RNA, and host proteins. Elucidating how receptor specificity and polymerasedriven replication affect the pathogenicity and transmission of H5N1 viruses will yield important clues about host adaptation, pandemic potential, and the development of antiviral drugs.

Transmissibility

What are the requirements for human-to-human transmission of a potentially pandemic highly pathogenic avian influenza virus, and what mechanisms are involved? The absence of efficient human-to-human transmission of H5N1 viruses to date may explain why the circulating avian influenza virus has not caused a pandemic. Ferrets, which are naturally susceptible to influenza, have been used as a model to investigate transmission of H5N1 viruses. In both humans and ferrets, respiratory epithelial cells express primarily α2,6-linked sialic acids, H5N1 viruses bind preferentially to epithelial cells in the lower respiratory tract, and infection causes acute respiratory illness (Matrosovich et al., 2004; Shinya et al., 2006; van Riel et al., 2007). Pathogenic H5N1 virus was not transmitted from infected to contact ferrets regardless of the α2,3- or α2,6-linked sialic acid receptor binding affinity (Yen et al., 2007b). In another study, acquisition of the surface glycoproteins of efficiently transmissible H3N2 human influenza viruses did not alter transmission of poorly transmissible H5N1 avian viruses (Maines et al., 2006), suggesting that H5N1 transmission involves multiple genetic adaptations.

Factors beyond the viral genome may also contribute to transmissibility. For example, virus is thought to be transmitted in droplets generated by coughing or sneezing. In a guinea pig model of human infection, H3N2 influenza virus was indeed transmitted via an aerosol, and aerosol transmission was enhanced by lower humidity and temperature (Lowen et al., 2007). These findings shed light on the seasonality of human influenza outbreaks. Importantly, however, H3N2 influenza virus is transmitted among guinea pigs without coughing and sneezing, which is not true in ferrets. If H5N1 viruses do acquire efficient human-to-human transmissibility, it will be important to understand the full range of factors that can modulate transmission.

Coinfection

The coinfection of a human by a seasonal H3N2 influenza virus with efficient transmissibility and an avian H5N1 virus with poor transmissibility has the potential to generate a reassortant H5N1 virus with efficient transmission or pandemic potential. In a hallmark study, the reassortant viruses generated from swapping the genes of H5N1 and H3N2 influenza viruses did not yield influenza viruses with efficient transmissibility in ferrets (Maines et al., 2006). Nevertheless, there is still concern about coinfection of humans and the emergence of H5N1 viruses with efficient human-to-human transmission.

Multiple different genotypes of avian H5N1 viruses continue to emerge and the possibility of coinfection of humans with both avian H5N1 and seasonal H1N1 or H3N2 influenza virus is a continuing possibility. The possibility of genetic reassortment between these influenza viruses resulting in an H5N1 virus with increased ability to transmit between humans indicates that increased surveillance is needed to capture these coinfections of H5N1 and other influenza viruses and to elucidate which genetic reassortments will result in an influenza virus with pandemic potential.

The contribution to pathogenesis of coinfections with influenza virus and bacteria is another intriguing research area. Evidence suggests that a majority of deaths during the 1918 Spanish flu pandemic were due to secondary bacterial pneumonia (McCullers, 2006; Morens et al., 2008). Major knowledge gaps exist in our understanding of the complex interactions of multiple pathogens with each other and with the coinfected host. Thus, research and pandemic preparedness will require a focus on secondary bacterial infection and treatment.

Host Factors in Pathogenicity

The Immune Response

The pathology induced by some strains of influenza A virus has been correlated with an excessive immune response (de Jong et al., 2006). Studies of innate immune cells (dendritic cells, monocytes, natural killer cells, and neutrophils) and of the CD4, CD8, and B lymphocytes during infection with H5N1 avian influenza virus are necessary to understand the protective and pathologic effects of the adaptive immune response and to inform the design of vaccines. The fundamental questions are the tissues in which these immune cells act, the effector functions they perform, and the requirements and mechanisms that regulate these functions.

The rapid accumulation of proinflammatory cytokines (“cytokine storm”) after infection, with either the currently circulating highly pathogenic avian influenza virus or the 1918 Spanish influenza virus, is thought to play a prominent role in morbidity and mortality (Cheung et al., 2002; de Jong et al., 2006; Kash et al., 2006b). Levels of mRNAs encoding TNFα, RANTES (regulated on activation, normal T cell expressed, and secreted), MIP1α and 1β (macrophage inflammatory protein), and CCL2 (monocyte chemotactic protein-1 MCP-1) were markedly higher in primary human macrophages infected with H5N1 virus than in those infected with human-adapted H3N2 or H1N1 viruses (Cheung et al., 2002). Similarly, primary human bronchial and alveolar epithelial cells secreted significantly more IP-10 (interferon-γ-inducible protein-10), IL6 (interleukin- 6), and RANTES when infected with H5N1 compared with H1N1 influenza virus (Chan et al., 2005). Mice and macaques infected with the 1918 pandemic strain of influenza virus showed increased expression of proinflammatory cytokine mRNAs and proteins (Kash et al., 2006b).

Because a dysregulated cytokine response has been linked to the severity of disease caused by some strains of influenza A virus, therapy that blocks the cytokine cascade could prove beneficial. Administration of an immunomodulatory statin, gemfibrozil, 4–10 days after inoculation with an H2N2

virus increased survival of mice by 50% (Budd et al., 2007). In another study, disruption of the TNFα signaling cascade in mice reduced morbidity after inoculation with the H5N1 avian influenza virus (Szretter et al., 2007). However, although survival was prolonged, mortality was not significantly reduced. Further, mice that lacked CCL2, IL6, or TNFα succumbed as often as wild-type mice to infection with a lethal H5N1 virus (Salomon et al., 2007). Interestingly, recent investigations into the role of cytokines in ferrets infected with the H5N1 virus indicated that treatment with a chemokine receptor inhibitor, AMG487, reduced morbidity and modestly delayed mortality (Cameron et al., 2008). Together, these results suggest that inhibition of a single immune signaling molecule is unlikely to improve morbidity or survival following infection with highly pathogenic avian influenza virus. However, therapies targeting an overexuberant immune response may yet prove beneficial. A more complete understanding of the cause and effect of the cytokine storm may aid in the development of new therapeutics (Table 1).

Table 1. Strategies for Vaccines and Antiviral Therapies

Vaccines	Antiviral Therapies
Techniques	
Inactivated vaccine	Neuraminidase inhibitors
Subunit vaccine	M2 ion channel blockers
Live attenuated vaccine	Monoclonal antibodies
DNA-based vaccine	Immunomodulatory therapy
Vector-based vaccine	siRNAs
Virus like particles	Sialic acid receptor cleavage/ sialidases
	Inhibitors of virus-induced signaling pathways
	Inhibitors of viral polymerase
Challenges	
Non-egg-based production	Emergence of resistance
Targeting generation of virus-specific CTLs	Timeframe of efficacy
Increasing immunogenicity and adjuvants	Stockpiling
Rapid production	Accessibility and affordability
Dosage	Dosage
Administration route	Administration route
Immune correlates of protection	Duration of therapy
	Combination therapy

Other Host Factors

Influenza virus encodes only ten viral proteins but replicates successfully in a broad range of avian and mammalian species by exploiting host cell functions (Figure 2). The interactions of the virus and host cell proteins are crucial to viral replication, assembly, and trafficking (Ludwig et al., 2006). Further understanding of the complex signal transduction pathways induced by viral and host protein interactions may provide new targets for antiviral therapy. The identity of the specific host factors involved in resistance and susceptibility to avian influenza virus can be solved only by the combined efforts of virologists, immunologists, geneticists, and biochemists.

We know that type I interferons (IFNα/β) are a crucial innate defense against viruses because of their potent antiviral and immunoregulatory effects. Mx1 is an antiviral host gene induced by IFNα/β, and inbred mouse models of influenza usually lack this gene. In two recent studies, these mice were protected from infection with lethal human H5N1 virus and from the reconstructed 1918 pandemic virus by a mechanism that reduces polymerase activity and is enhanced by IFNα/β (Tumpey et al., 2007). Further research into this protective mechanism may reveal how it can be exploited therapeutically.

A key component of innate immunity is pattern recognition receptors, some of which specifically detect viral components. One such receptor, retinoic acid-inducible protein I (RIG-I), was recently implicated in the recognition of influenza RNA and the activation of antiviral pathways. This protein is crucial for production of IFNα/β in response to influenza, and mice genetically deficient in RIG-I show increased susceptibility to influenza. RIG-I specifically recognizes 5′-phosphorylated viral genomic single-stranded RNA. However, the nonstructural NS1 protein of influenza virus has multiple functions including inhibiting the host immune response by forming a complex with RIG-I and blocking the induction of type I interferons (Pichlmair et al., 2006). Further investigation of these innate sensors and the host cofactors involved in inducing the anti-influenza virus response is needed. A point of interest is whether the highly lethal H5N1 viruses and other influenza viruses with pandemic potential have mechanisms to reduce the effectiveness of innate immune sensors.

Another host factor inhibited by the NS1 protein of influenza A is CPSF30 (cleavage and polyadenylation specificity factor), which is required for processing of cellular pre-mRNAs including IFNβ mRNA. Recent structural data suggest that drugs targeting the interaction of CPSF30 and NS1 may be useful in the treatment of influenza (Das et al., 2008). Other interferoninduced host factors involved in protection against influenza viruses include 2′-5′ oligo (A) synthetase and protein kinase R. The cellular signal transduction pathways activated during infection with highly pathogenic avian influenza virus need further elucidation to reveal the key biochemical mechanisms that are important during infection (Kash et al., 2006a; Ludwig et al., 2006). Although Mx1, RIG-I, CPSF30, 2′-5′ oligo (A) synthetase, and protein kinase R have clear roles in the host response to influenza viruses, many other host factors that affect resistance or susceptibility to these viruses probably remain to be discovered.

Recent innovative work reveals host factors that are involved specifically in influenza virus replication (Hao et al., 2008). Priority should be given to

identifying these factors, some of which may explain the elevated pathogenicity or the absence of transmission observed in certain populations.

Rapid Viral Evolution

The Moving Vaccine Target

The rapid evolution of the influenza A viruses continually complicates the effective use of vaccines and therapies. Because these genomically unstable negative-strand RNA viruses change so rapidly, vaccine strains can quickly become outdated and the lengthy, labor-intensive, large-scale production of vaccines in eggs is problematic. The time lag between vaccine production and seasonal flu outbreaks (often 6 months or more) can result in a mismatch between the vaccine and the circulating virus. During the 2007–2008 flu season, a mismatch in the seasonal influenza vaccine caused an increase in childhood deaths from influenza in the Northern Hemisphere. The outdated technology used to prepare vaccine strains and to mass-produce vaccines urgently requires modernizing (Table 1). Much research has been focused on alternative vaccine production systems. The plasmid-based reverse genetics system has been used to generate reference viruses for H5N1 vaccines. In addition, there have been promising advances in the development of vector, DNA, recombinant subunit, peptidebased, and virus-like particle vaccines (Subbarao and Joseph,2007).

Lack of Immune Correlates of Vaccine Protection

How do vaccines mediate immune protection? Protection does not correlate with neutralizing antibodies after vaccination against H5N1 viruses, as it usually does after receipt of the seasonal influenza vaccine. Further, vaccines of different H5N1 clades and subtypes appear to offer crossprotection (Govorkova et al., 2006). Importantly, in the case of a pandemic, crossprotection may allow a minimum amount of vaccine to be used per person or may expand the pool of vaccine candidates. It is therefore essential to determine the mechanisms and factors required for crossprotection, including the contributions of T cell-mediated immunity and serum and mucosal antibodies. Questions also remain about which vaccination methods (e.g., intact virus versus subunit vaccines; use of adjuvants; number, dose, and route of inoculations) will reduce the amount of vaccine needed (Leroux-Roels et al., 2007). Research should also focus on resolving how age (particularly from the point of view of children and the elderly) affects vaccine efficacy and immune correlates of protection.

New strategies to induce immune protection against highly pathogenic avian influenza virus must be explored. Vaccines based on proteins other than the surface glycoproteins, such as the matrix segment, have demonstrated some protective potential (Watanabe et al., 2007). Basic research into the mechanisms of the innate and adaptive immune responses to avian influenza virus will provide the cornerstone for the development of optimally protective vaccines. Protection is currently gauged primarily by the production of neutralizing antibodies, although there is great variation in assay standards and, for certain viruses, poor correlation between the assay results and the level of protection. It is generally agreed that better immunecorrelates for testing vaccine efficacy are needed.

A long-standing question is whether a single vaccine could protect against influenza viruses of different subtypes. Rather than focusing on the production of neutralizing antibodies, immunologists hope to generate a vaccine that activates virus-specific cytotoxic T lymphocytes (CTLs) directed toward epitopes conserved among influenza virus subtypes. A subset of epitopes recognized by human CTLs is highly conserved among human and avian H5N1 influenza A viruses; these epitopes are on internal influenza proteins, which are less susceptible to antigenic variation (Wang et al., 2007). However, it remains to be determined how an activated T cell population could be maintained in the lungs without inducing autoimmunity. Crossreactive vaccines that activate CTLs would be a valuable tool for controlling avian influenza viruses with pandemic potential (Rimmelzwaan et al., 2007).

Vaccine Use in Domestic Poultry

Vaccination to control the H5N1 virus in domestic poultry is controversial because of concerns that it may drive antigenic drift or mask the continued circulation of virus. However, the benefit of vaccinating poultry has been dramatically illustrated in Vietnam. By 2005, 90 humans in Vietnam had been infected with the avian influenza virus H5N1 and 39 had died. After widespread vaccination of domestic poultry, infection of humans and domestic chickens ceased. The H5N1 virus re-emerged in humans and poultry in Vietnam in 2007 due to the difficulty of maintaining poultry vaccinations, effectively immunizing domestic ducks, and controlling poultry smuggling. A program requiring vaccination of all poultry entering Hong Kong was successful for 7 years but is now less effective because the vaccine needs to be updated.

Although poultry vaccination is an important tool for control of the H5N1 virus, the ultimate goal is eradication of this virus and cessation of vaccine use. Continued vaccination promotes endemic persistence of the H5N1 virus in domestic poultry and may mask the presence of highly pathogenic strains. The absence of global standards for the antigenic content of poultry vaccines is an unresolved problem, although the antigen dose required to induce protection and prevent virus spread in different breeds of domestic fowl is easily determined. More significantly, it remains unresolved whether standardized vaccination or vaccination of immunocompromised animals promote selection of more pathogenic variants of avian influenza virus. More information is needed about the immunobiology of avian species to determine the best use of poultry vaccines.

Antiviral Therapies

The anti-influenza drugs approved for clinical use are the neuraminidase inhibitors (orally administered oseltamivir trade name Tamiflu and inhaled zanamivir trade name Relenza) and inhibitors of the viral M2 matrix protein ion channels (the adamantanes, amantadine, and rimantadine). Several other neuraminidase inhibitors (peramivir; pyrrolidine derivative A315675; and long-acting R-118958 and FLUNET compounds) are under development. Oseltamivir is effective against many avian influenza virus strains in animal models, although an optimal treatment schedule may be required for highly virulent viruses (Govorkova et al., 2007). Information about drug efficacy in humans is

limited; treatment often starts late in the course of infection, and the dosage and duration of treatment are often suboptimal (Beigel et al., 2005).

The emergence of drug-resistant virus variants is one of the disadvantages of antiviral therapy. Most clade 1 H5N1 influenza viruses are now resistant to adamantanes (Hayden, 2006). Resistance to the neuraminidase inhibitors appears to be less of a problem, although oseltamivir-resistant viruses with neuraminidase mutations (H274Y and N294S) have been isolated from patients during and before drug treatment (Le et al., 2005). Further, resistant variants carrying either of these neuraminidase mutations may retain their high pathogenicity in mammalian species (Yen et al., 2007a). Emerging resistance to antivirals is of increasing concern as H1N1 seasonal influenza viruses resistant to oseltamivir appeared in the 2007–2008 flu season (Lackenby et al., 2008) and have become prevalent in the 2008–2009 influenza season. Given that neuraminidase inhibitors are the most commonly prescribed for seasonal influenza and are being stockpiled in case of an influenza pandemic, it is imperative to understand how and why these drug-resistant influenza viruses are maintaining transmissibility and virulence. Improved approaches to antiviral drug use may include development of new antivirals, using combinations of antivirals, or optimizing existing antiviral drug regimens (dosage, duration, route of administration).

Given increasing evidence that resistance to the conventional antivirals emerges rapidly, there is an urgent need to identify new therapeutic targets. Viral polymerase activity may offer such a target, in view of the correlation between the lethality and rapid replication of certain avian influenza virus strains. Small-interfering RNAs against the genes encoding nucleoprotein or polymerase protein PA of the viral replication complex reduced virus replication and increased the survival of lethally challenged hosts (Tompkins et al., 2004). The screening of small inhibitory molecules using high-throughput viral replication assays will advance the field of anti-influenza therapy. Ribavirin and its analog viramidine, which inhibit virusencoded RNA polymerases, may also reduce the replication efficiency of H5N1 viruses. The sialidase fusion construct DAS181 (Fludase) was recently shown to cleave sialic acid receptors for both human and avian influenza viruses and to provide a potent anti-H5N1 therapeutic effect in infected mice (Belser et al., 2007).

In the search for protective agents, some researchers have focused on familiar anti-inflammatory drugs, including statins (Fedson, 2006). Neutralizing antibodies are also being pursued as a treatment strategy. Neutralizing anti-H5N1 human monoclonal antibodies provide effective prophylaxis and therapy in mice (Hanson et al., 2006; Simmons et al., 2007). Such neutralizing crossreactive antibodies or other immunotherapies are promising avenues for treating humans infected with the H5N1influenza virus.

Pandemic Preparedness

Influenza does not recognize man-made borders, and it is debatable whether any country should lay claim to strains of influenza virus isolated there. However, a country that shares its influenza virus isolates for global research is entitled to the benefits derived, especially if an emerging pathogen is killing its

citizens. How such competing claims are to be balanced must be resolved by the World Health Organization. The core issues are ultimate ownership of the isolated viruses and associated intellectual property, and the fair distribution of vaccines derived from those viruses. Such proprietary claims conflict with the global sharing of influenza viruses and their genomic information, vaccines, and antiviral drug sensitivity data required for optimal pandemic preparedness. These issues are under intensive review by international organizations seeking to ensure that developing countries will have access to vaccines and anti-influenza drugs derived from viruses isolated within their borders and will be informed of the distribution of those viruses and their derivatives.

Pandemic preparedness is an ongoing process that continually incorporates emerging information. Most countries have pandemic plans, but their effectiveness will depend on availability of the expanding knowledge base to veterinary and public health officials, the transfer of knowledge to industry, and ongoing communication with leaders in commerce, industry, and transportation.

There is concern that if an H5N1 pandemic does not occur, scientists will lose public credibility and pandemic planning will be supplanted by more pressing public health programs. Scientists have alerted the public to observations that call for special vigilance. However, an influenza pandemic is no more predictable than the human use of biological pathogens or chemical agents. Nations can help to ensure the sustainability of their preparedness programs by establishing permanent pandemic planning staff positions in their health and security departments.

The stockpiling of antiviral agents is an important element of influenza pandemic planning, but the stability of the active ingredients, capsules, and inert carrier components must be monitored. Oseltamivir appears to be extremely stable (Monto et al., 2006). It would be unrealistic to consider replacement of stockpiled drugs, but their stable components could be recycled. Are pandemic planners making arrangements for the maintenance of these valuable national resources? Although the H5N1 avian influenza virus may never acquire full human pandemic potential, another influenza virus certainly will. Antiinfluenza drugs will remain our first line of defense.

Although it is currently impossible to predict which influenza virus will cause the next epidemic or pandemic, the pathogenic potential of these viruses can be anticipated more precisely with continued research and development in surveillance, diagnostics, and genomic studies of the virus and its key hosts.

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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008

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Summary

This report updates the 2007 recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine and antiviral agents (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2007;56[No. RR-6]). The 2008 recommendations include new and updated information. Principal updates and changes include 1) a new recommendation that annual vaccination be administered to all children aged 5--18 years, beginning in the 2008--09 influenza season, if feasible, but no later than the 2009--10 influenza season; 2) a recommendation that annual vaccination of all children aged 6 months through 4 years (59 months) continue to be a primary focus of vaccination efforts because these children are at higher risk for influenza complications compared with older children; 3) a new recommendation that either trivalent inactivated influenza vaccine or live, attenuated influenza vaccine (LAIV) be used when vaccinating healthy persons aged 2 through 49

years (the previous recommendation was to administer LAIV to person aged 5--49 years); 4) a recommendation that vaccines containing the 2008--09 trivalent vaccine virus strains A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens be used; and, 5) new information on antiviral resistance among influenza viruses in the United States. Persons for whom vaccination is recommended are listed in boxes 1 and 2. These recommendations also include a summary of safety data for U.S. licensed influenza vaccines. This report and other information are available at CDC's influenza website (http://www.cdc.gov/flu), including any updates or supplements to these recommendations that might be required during the 2008--09 influenza season. Vaccination and health-care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information.

Introduction

In the United States, annual epidemics of influenza occur typically during the late fall through early spring seasons. Influenza viruses can cause disease among persons in any age group, but rates of infection are highest among children (*1--3*). Rates of serious illness and death are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza (*1,4,5*). An annual average of approximately 36,000 deaths during 1990--1999 and 226,000 hospitalizations during 1979--2001 have been associated with influenza epidemics (*6,7*).

Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications. Influenza vaccine can be administered to any person aged ≥6 months (who does not have contraindications to vaccination) to reduce the likelihood of becoming ill with influenza or of transmitting influenza to others. Trivalent inactivated influenza vaccine (TIV) can be used for any person aged ≥6 months, including those with high-risk conditions (Boxes 1 and 2). Live, attenuated influenza vaccine (LAIV) may be used for healthy, nonpregnant persons aged 2--49 years. If vaccine supply is limited, priority for vaccination is typically assigned to persons in specific groups and of specific ages who are, or are contacts of, persons at higher risk for influenza complications. Because the safety or effectiveness of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications, these persons should only be vaccinated with TIV. Influenza viruses undergo frequent antigenic change (i.e., antigenic drift), and persons recommended for vaccination must receive an annual vaccination against the influenza viruses forecasted to be in circulation. Although vaccination coverage has increased in recent years for many groups targeted for routine vaccination, coverage remains low among most of these groups, and strategies to improve vaccination coverage, including use of

reminder/recall systems and standing orders programs, should be implemented or expanded.

Antiviral medications are an adjunct to vaccination and are effective when administered as treatment and when used for chemoprophylaxis after an exposure to influenza virus. Oseltamivir and zanamivir are the only antiviral medications recommended for use in the United States. Amantadine or rimantidine should not be used for the treatment or prevention of influenza in the United States until evidence of susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses.

Methods

CDC's Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Vaccine Working Group* meets monthly throughout the year to discuss newly published studies, review current guidelines, and consider potential revisions to the recommendations. As they review the annual recommendations for ACIP consideration of the full committee, members of the working group consider a variety of issues, including burden of influenza illness, vaccine effectiveness, safety and coverage in groups recommended for vaccination, feasibility, cost-effectiveness, and anticipated vaccine supply. Working group members also request periodic updates on vaccine and antiviral production, supply, safety and efficacy from vaccinologists, epidemiologists, and manufacturers. State and local vaccination program representatives are consulted. Influenza surveillance and antiviral resistance data were obtained from CDC's Influenza Division. The Vaccines and Related Biological Products Advisory Committee provides advice on vaccine strain selection to the Food and Drug Administration (FDA), which selects the viral strains to be used in the annual trivalent influenza vaccines.

Published, peer-reviewed studies are the primary source of data used by ACIP in making recommendations for the prevention and control of influenza, but unpublished data that are relevant to issues under discussion also might be considered. Among studies discussed or cited, those of greatest scientific quality and those that measured influenza-specific outcomes are the most influential. For example, population-based estimates that use outcomes associated with laboratory-confirmed influenza virus infection outcomes contribute the most specific data for estimates of influenza burden. The best evidence for vaccine or antiviral efficacy and effectiveness comes from randomized controlled trials that assess laboratory-confirmed influenza infections as an outcome measure and consider factors such as timing and intensity of influenza circulation and degree of match between vaccine strains and wild circulating strains (*8,9*). Randomized, placebo-controlled trials cannot be performed ethically in populations for which vaccination already is

recommended, but observational studies that assess outcomes associated with laboratory-confirmed influenza infection can provide important vaccine or antiviral effectiveness data. Randomized, placebo-controlled clinical trials are the best source of vaccine and antiviral safety data for common adverse events; however, such studies do not have the power to identify rare but potentially serious adverse events. The frequency of rare adverse events that might be associated with vaccination or antiviral treatment is best assessed by retrospective reviews of computerized medical records from large linked clinical databases, and by reviewing medical charts of persons who are identified as having a potential adverse event after vaccination (*10,11*). Vaccine coverage data from a nationally representative, randomly selected population that includes verification of vaccination through health-care record review is superior to coverage data derived from limited populations or without verification of vaccination but is rarely available for older children or adults (*12*). Finally, studies that assess vaccination program practices that improve vaccination coverage are most influential in formulating recommendations if the study design includes a nonintervention comparison group. In cited studies that included statistical comparisons, a difference was considered to be statistically significant if the p-value was <0.05 or the 95% confidence interval (CI) around an estimate of effect allowed rejection of the null hypothesis (i.e., no effect).

These recommendations were presented to the full ACIP and approved in February 2008. Modifications were made to the ACIP statement during the subsequent review process at CDC to update and clarify wording in the document. Data presented in this report were current as of July 1, 2008. Further updates, if needed, will be posted at CDC's influenza website (http://www.cdc.gov/flu).

Primary Changes and Updates in the Recommendations

The 2008 recommendations include five principal changes or updates:

- Beginning with the 2008--09 influenza season, annual vaccination of all children aged 5--18 years is recommended. Annual vaccination of all children aged 5--18 years should begin in September or as soon as vaccine is available for the 2008--09 influenza season, if feasible, but annual vaccination of all children aged 5--18 years should begin no later than during the 2009--10 influenza season.
- Annual vaccination of all children aged 6 months--4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue. Children and adolescents at high risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children.
- Either TIV or LAIV can be used when vaccinating healthy persons aged 2--49 years. Children aged 6 months--8 years should receive 2 doses of vaccine if they have not been vaccinated previously at any time with

either LAIV or TIV (doses separated by ≥4 weeks); 2 doses are required for protection in these children. Children aged 6 months--8 years who received only 1 dose in their first year of vaccination should receive 2 doses the following year. LAIV should not be administered to children aged <5 years with possible reactive airways disease, such as those who have had recurrent wheezing or a recent wheezing episode. Children with possible reactive airways disease, persons at higher risk for influenza complications because of underlying medical conditions, children aged 6--23 months, and persons aged >49 years should receive TIV.

- The 2008--09 trivalent vaccine virus strains are A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens.

Oseltamivir-resistant influenza A (H1N1) strains have been identified in the United States and some other countries. However, oseltamivir or zanamivir continue to be the recommended antivirals for treatment of influenza because other influenza virus strains remain sensitive to oseltamivir, and resistance levels to other antiviral medications remain high.

Background and Epidemiology

Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A viruses are categorized into subtypes on the basis of two surface antigens: hemagglutinin and neuraminidase. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have circulated globally. Influenza A (H1N2) viruses that probably emerged after genetic reassortment between human A (H3N2) and A (H1N1) viruses also have been identified in some influenza seasons. Both influenza A subtypes and B viruses are further separated into groups on the basis of antigenic similarities. New influenza virus variants result from frequent antigenic change (i.e., antigenic drift) resulting from point mutations that occur during viral replication (*13*).

Currently circulating influenza B viruses are separated into two distinct genetic lineages (Yamagata and Victoria) but are not categorized into subtypes. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses. Influenza B viruses from both lineages have circulated in most recent influenza seasons (*13*).

Immunity to the surface antigens, particularly the hemagglutinin, reduces the likelihood of infection (*14*). Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype of influenza virus. Furthermore, antibody to one antigenic type or subtype of influenza virus might not protect against infection with a new antigenic variant of the same type or subtype (*15*). Frequent emergence of antigenic variants through antigenic

drift is the virologic basis for seasonal epidemics and is the reason for annually reassessing the need to change one or more of the recommended strains for influenza vaccines.

More dramatic changes, or antigenic shifts, occur less frequently. Antigenic shift occurs when a new subtype of influenza A virus appears and can result in the emergence of a novel influenza A virus with the potential to cause a pandemic. New influenza A subtypes have the potential to cause a pandemic when they are able to cause human illness and demonstrate efficient human-to-human transmission and there is little or no previously existing immunity among humans (*13*).

Clinical Signs and Symptoms of Influenza

Influenza viruses are spread from person to person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person) (*16*). Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets do not remain suspended in the air and generally travel only a short distance (≤1 meter) through the air. Contact with respiratory-droplet contaminated surfaces is another possible source of transmission. Airborne transmission (via small-particle residue [≤5µm] of evaporated droplets that might remain suspended in the air for long periods of time) also is thought to be possible, although data supporting airborne transmission are limited (*16*--*21*). The typical incubation period for influenza is 1--4 days (average: 2 days) (*13*). Adults shed influenza virus from the day before symptoms begin through 5--10 days after illness onset (*22,23*). However, the amount of virus shed, and presumably infectivity, decreases rapidly by 3--5 days after onset in an experimental human infection model (*24,25*). Young children also might shed virus several days before illness onset, and children can be infectious for ≥10 days after onset of symptoms (*26*). Severely immunocompromised persons can shed virus for weeks or months (*27*--*30*).

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis) (*31*). Among children, otitis media, nausea, and vomiting also are commonly reported with influenza illness (*32,33*). Uncomplicated influenza illness typically resolves after 3--7 days for the majority of persons, although cough and malaise can persist for >2 weeks. However, influenza virus infections can cause primary influenza viral pneumonia; exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease); lead to secondary bacterial pneumonia, sinusitis, or otitis media; or contribute to coinfections with other viral or bacterial pathogens (*34*--*36*). Young children with influenza virus infection might have initial symptoms

mimicking bacterial sepsis with high fevers (*35*--*38*), and febrile seizures have been reported in 6%--20% of children hospitalized with influenza virus infection (*32,35,39*). Population-based studies among hospitalized children with laboratory-confirmed influenza have demonstrated that although the majority of hospitalizations are brief (≤2 days), 4%--11% of children hospitalized with laboratory-confirmed influenza required treatment in the intensive care unit, and 3% required mechanical ventilation (*35,37*). Among 1,308 hospitalized children in one study, 80% were aged <5 years, and 27% were aged <6 months (*35*). Influenza virus infection also has been uncommonly associated with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome (*32,34,40,41*).

Respiratory illnesses caused by influenza virus infection are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of signs and symptoms alone. Sensitivity and predictive value of clinical definitions vary, depending on the prevalence of other respiratory pathogens and the level of influenza activity (*42*). Among generally healthy older adolescents and adults living in areas with confirmed influenza virus circulation, estimates of the positive predictive value of a simple clinical definition of influenza (acute onset of cough and fever) for laboratory-confirmed influenza infection have varied (range: 79%--88%) (*43,44*).

Young children are less likely to report typical influenza symptoms (e.g., fever and cough). In studies conducted among children aged 5--12 years, the positive predictive value of fever and cough together was 71%--83%, compared with 64% among children aged <5 years (*45*). In one large, population-based surveillance study in which all children with fever or symptoms of acute respiratory tract infection were tested for influenza, 70% of hospitalized children aged <6 months with laboratory-confirmed influenza were reported to have fever and cough, compared with 91% of hospitalized children aged 6 months--5 years. Among children who subsequently were shown to have laboratory-confirmed influenza infections, only 28% of those hospitalized and 17% of those treated as outpatients had a discharge diagnosis of influenza (*38*).

Clinical definitions have performed poorly in some studies of older patients. A study of nonhospitalized patients aged ≥60 years indicated that the presence of fever, cough, and acute onset had a positive predictive value of 30% for influenza (*46*). Among hospitalized patients aged ≥65 years with chronic cardiopulmonary disease, a combination of fever, cough, and illness of <7 days had a positive predictive value of 53% for confirmed influenza infection (*47*). In addition, the absence of symptoms of influenza-like illness (ILI) does not effectively rule out influenza; among hospitalized adults with laboratory-confirmed infection in two studies, 44%--51% had typical ILI symptoms (*48,49*). A study of vaccinated older persons with chronic lung disease reported that

cough was not predictive of laboratory-confirmed influenza virus infection, although having both fever or feverishness and myalgia had a positive predictive value of 41% (*50*). These results highlight the challenges of identifying influenza illness in the absence of laboratory confirmation and indicate that the diagnosis of influenza should be considered in patients with respiratory symptoms or fever during influenza season.

Health-Care Use, Hospitalizations, and Deaths Attributed to Influenza

In the United States, annual epidemics of influenza typically occur during the fall or winter months, but the peak of influenza activity can occur as late as April or May (Figure 1). Influenza-related complications requiring urgent medical care, including hospitalizations or deaths, can result from the direct effects of influenza virus infection, from complications associated with age or pregnancy, or from complications of underlying cardiopulmonary conditions or other chronic diseases. Studies that have measured rates of a clinical outcome without a laboratory confirmation of influenza virus infection (e.g., respiratory illness requiring hospitalization during influenza season) to assess the effect of influenza can be difficult to interpret because of circulation of other respiratory pathogens (e.g., respiratory syncytial virus) during the same time as influenza viruses (*51*--*53*).

During seasonal influenza epidemics from 1979--1980 through 2000--2001, the estimated annual overall number of influenza-associated hospitalizations in the United States ranged from approximately 55,000 to 431,000 per annual epidemic (mean: 226,000) (*7*). The estimated annual number of deaths attributed to influenza from the 1990--91 influenza season through 1998--99 ranged from 17,000 to 51,000 per epidemic (mean: 36,000) (*6*). In the United States, the estimated number of influenza-associated deaths increased during 1990--1999. This increase was attributed in part to the substantial increase in the number of persons aged ≥65 years who were at increased risk for death from influenza complications (*6*). In one study, an average of approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976--1990, compared with an average of approximately 36,000 deaths per season during 1990--1999 (*6*). In addition, influenza A (H3N2) viruses, which have been associated with higher mortality (*54*), predominated in 90% of influenza seasons during 1990--1999, compared with 57% of seasons during 1976--1990 (*6*).

Influenza viruses cause disease among persons in all age groups (*1*--*5*). Rates of infection are highest among children, but the risks for complications, hospitalizations, and deaths from influenza are higher among persons aged ≥65 years, young children, and persons of any age who have medical conditions that place them at increased risk for complications from influenza (*1,4,5,55*--*58*).

Estimated rates of influenza-associated hospitalizations and deaths varied substantially by age group in studies conducted during different influenza epidemics. During 1990--1999, estimated average rates of influenza-associated pulmonary and circulatory deaths per 100,000 persons were 0.4--0.6 among persons aged 0--49 years, 7.5 among persons aged 50--64 years, and 98.3 among persons aged ≥65 years (*6*).

Children

Among children aged <5 years, influenza-related illness is a common cause of visits to medical practices and emergency departments. During two influenza seasons (2002--03 and 2003--04), the percentage of visits among children aged <5 years with acute respiratory illness or fever caused by laboratory-confirmed influenza ranged from 10%--19% of medical office visits to 6%--29% of emergency departments visits during the influenza season. Using these data, the rate of visits to medical clinics for influenza was estimated to be 50--95 per 1,000 children, and to emergency departments 6--27 per 1,000 children (*38*). Retrospective studies using medical records data have demonstrated similar rates of illness among children aged <5 years during other influenza seasons (*33,56,59*). During the influenza season, an estimated 7--12 additional outpatient visits and 5--7 additional antibiotic prescriptions per 100 children aged <15 years has been documented when compared with periods when influenza viruses are not circulating, with rates decreasing with increasing age of the child (*59*). During 1993--2004 in the Boston area, the rate of emergency department visits for respiratory illness that was attributed to influenza virus based on viral surveillance data among children aged ≤7 years during the winter respiratory illness season ranged from 22.0 per 1000 children aged 6--23 months to 5.4 per 1000 children aged 5--7 years (*60*).

Rates of influenza-associated hospitalization are substantially higher among infants and young children than among older children when influenza viruses are in circulation (Figure 2) and are similar to rates for other groups considered at high risk for influenza-related complications (*61--66*), including persons aged ≥65 years (*59,63*). During 1979--2001, the estimated rate of influenza-associated hospitalizations, using a national sample of hospital discharges of influenza-associated hospitalizations in the United States among children aged <5 years, was 108 hospitalizations per 100,000 person-years (*7*). Recent population-based studies that measured hospitalization rates for laboratory-confirmed influenza in young children documented hospitalization rates that are similar to or higher than rates derived from studies that analyzed hospital discharge data (*33,35,36,38,65*). Annual hospitalization rates for laboratory-confirmed influenza decrease with increasing age, ranging from 240--720 per 100,000 children aged <6 months to approximately 20 per 100,000 children aged 2--5 years (*38*). Hospitalization rates for children aged <5 years with high-

risk medical conditions are approximately 250--500 per 100,000 children (*56,58,67*).

Influenza-associated deaths are uncommon among children. An estimated annual average of 92 influenza-related deaths (0.4 deaths per 100,000 persons) occurred among children aged <5 years during the 1990s, compared with 32,651 deaths (98.3 per 100,000 persons) among adults aged ≥65 years (*6*). Of 153 laboratory-confirmed influenza-related pediatric deaths reported during the 2003--04 influenza season, 96 (63%) deaths occurred among children aged <5 years and 61 (40%) among children aged <2 years. Among the 149 children who died and for whom information on underlying health status was available, 100 (67%) did not have an underlying medical condition that was an indication for vaccination at that time (*68*). In California during the 2003--04 and 2004--05 influenza seasons, 51% of children with laboratory-confirmed influenza who died and 40% of those who required admission to an intensive care unit had no underlying medical conditions (*69*). These data indicate that although deaths are more common among children with risk factors for influenza complications, the majority of pediatric deaths occur among children of all age groups with no known high-risk conditions. The annual number of deaths among children reported to CDC for the past four influenza seasons has ranged from 84 during 2004--05 to 84 during 2007--08 (CDC, unpublished data, 2008).

Death associated with laboratory-confirmed influenza virus infection among children (defined as persons aged <18 years) is a nationally reportable condition. Deaths among children that have been attributed to co-infection with influenza and *Staphylococcus aureus*, particularly methicillin resistant *S. aureus* (MRSA), have increased during the preceding four influenza seasons (*70*; CDC, unpublished data, 2008). The reason for this increase is not established but might reflect an increasing prevalence within the general population of colonization with MRSA strains, some of which carry certain virulence factors (*71,72*).

Adults

Hospitalization rates during the influenza season are substantially increased for persons aged ≥65 years. One retrospective analysis based on data from managed-care organizations collected during 1996--2000 estimated that the risk during influenza season among persons aged ≥65 years with underlying conditions that put them at risk for influenza-related complications (i.e., one or more of the conditions listed as indications for vaccination) was approximately 560 influenza-associated hospitalizations per 100,000 persons, compared with approximately 190 per 100,000 healthy elderly persons. Persons aged 50--64 years with underlying medical conditions also were at substantially increased risk for hospitalizations during influenza season, compared with healthy adults

aged 50--64 years. No increased risk for influenza-associated hospitalizations was demonstrated among healthy adults aged 50--64 years or among those aged 19--49 years, regardless of underlying medical conditions (*64*).

Influenza is an important contributor to the annual increase in deaths attributed to pneumonia and influenza that is observed during the winter months (Figure 3). During 1976--2001, an estimated yearly average of 32,651 (90%) influenza-related deaths occurred among adults aged ≥65 years (*6*). Risk for influenza-associated death was highest among the oldest elderly, with persons aged ≥85 years 16 times more likely to die from an influenza-associated illness than persons aged 65--69 years (*6*).

The duration of influenza symptoms is prolonged and the severity of influenza illness increased among persons with human immunodeficiency virus (HIV) infection (*73--77*). A retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than it was either before or after influenza was circulating. The risk for hospitalization was higher for HIV-infected women than it was for women with other underlying medical conditions (*78*). Another study estimated that the risk for influenza-related death was 94--146 deaths per 100,000 persons with acquired immunodeficiency syndrome (AIDS), compared with 0.9--1.0 deaths per 100,000 persons aged 25--54 years and 64--70 deaths per 100,000 persons aged ≥65 years in the general population (*79*).

Influenza-associated excess deaths among pregnant women were reported during the pandemics of 1918--1919 and 1957--1958 (*80--83*). Case reports and several epidemiologic studies also indicate that pregnancy increases the risk for influenza complications (*84--89*) for the mother. The majority of studies that have attempted to assess the effect of influenza on pregnant women have measured changes in excess hospitalizations for respiratory illness during influenza season but not laboratory-confirmed influenza hospitalizations. Pregnant women have an increased number of medical visits for respiratory illnesses during influenza season compared with nonpregnant women (*90*). Hospitalized pregnant women with respiratory illness during influenza season have increased lengths of stay compared with hospitalized pregnant women without respiratory illness. Rates of hospitalization for respiratory illness were twice as common during influenza season (*91*). A retrospective cohort study of approximately 134,000 pregnant women conducted in Nova Scotia during 1990--2002 compared medical record data for pregnant women to data from the same women during the year before pregnancy. Among pregnant women, 0.4% were hospitalized and 25% visited a clinician during pregnancy for a respiratory illness. The rate of third-trimester hospital admissions during the influenza season was five times higher than the rate during the influenza season in the

year before pregnancy and more than twice as high as the rate during the noninfluenza season. An excess of 1,210 hospital admissions in the third trimester per 100,000 pregnant women with comorbidities and 68 admissions per 100,000 women without comorbidities was reported (*92*). In one study, pregnant women with respiratory hospitalizations did not have an increase in adverse perinatal outcomes or delivery complications (*93*); however, another study indicated an increase in delivery complications (*91*). However, infants born to women with laboratory-confirmed influenza during pregnancy do not have higher rates of low birth weight, congenital abnormalities, or low Apgar scores compared with infants born to uninfected women (*88,94*).

Options for Controlling Influenza

The most effective strategy for preventing influenza is annual vaccination. Strategies that focus on providing routine vaccination to persons at higher risk for influenza complications have long been recommended, although coverage among the majority of these groups remains low. Routine vaccination of certain persons (e.g., children, contacts of persons at risk for influenza complications, and HCP) who serve as a source of influenza virus transmission might provide additional protection to persons at risk for influenza complications and reduce the overall influenza burden, but coverage levels among these persons needs to be increased before effects on transmission can be reliably measured. Antiviral drugs used for chemoprophylaxis or treatment of influenza are adjuncts to vaccine but are not substitutes for annual vaccination. However, antiviral drugs might be underused among those hospitalized with influenza (*95*). Nonpharmacologic interventions (e.g., advising frequent handwashing and improved respiratory hygiene) are reasonable and inexpensive; these strategies have been demonstrated to reduce respiratory diseases (*96,97*) but have not been studied adequately to determine if they reduce transmission of influenza virus. Similarly, few data are available to assess the effects of community-level respiratory disease mitigation strategies (e.g., closing schools, avoiding mass gatherings, or using respiratory protection) on reducing influenza virus transmission during typical seasonal influenza epidemics (*98,99*).

Influenza Vaccine Efficacy, Effectiveness, and Safety

Evaluating Influenza Vaccine Efficacy and Effectiveness Studies

The efficacy (i.e., prevention of illness among vaccinated persons in controlled trials) and effectiveness (i.e., prevention of illness in vaccinated populations) of influenza vaccines depend in part on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation (see Effectiveness of Influenza Vaccination when Circulating Influenza Virus Strains Differ from Vaccine Strains), and the outcome being measured. Influenza vaccine efficacy and effectiveness studies

have used multiple possible outcome measures, including the prevention of medically attended acute respiratory illness (MAARI), prevention of laboratory-confirmed influenza virus illness, prevention of influenza or pneumonia-associated hospitalizations or deaths, or prevention of seroconversion to circulating influenza virus strains. Efficacy or effectiveness for more specific outcomes such as laboratory-confirmed influenza typically will be higher than for less specific outcomes such as MAARI because the causes of MAARI include infections with other pathogens that influenza vaccination would not be expected to prevent (*100*). Observational studies that compare less-specific outcomes among vaccinated populations to those among unvaccinated populations are subject to biases that are difficult to control for during analyses. For example, an observational study that determines that influenza vaccination reduces overall mortality might be biased if healthier persons in the study are more likely to be vaccinated (*101,102*). Randomized controlled trials that measure laboratory-confirmed influenza virus infections as the outcome are the most persuasive evidence of vaccine efficacy, but such trials cannot be conducted ethically among groups recommended to receive vaccine annually.

Influenza Vaccine Composition

Both LAIV and TIV contain strains of influenza viruses that are antigenically equivalent to the annually recommended strains: one influenza A (H3N2) virus, one influenza A (H1N1) virus, and one influenza B virus. Each year, one or more virus strains in the vaccine might be changed on the basis of global surveillance for influenza viruses and the emergence and spread of new strains. All three vaccine virus strains were changed for the recommended vaccine for the 2008--09 influenza season, compared with the 2007--08 season (see Recommendations for Using TIV and LAIV During the 2008--09 Influenza Season). Viruses for both types of currently licensed vaccines are grown in eggs. Both vaccines are administered annually to provide optimal protection against influenza virus infection (Table 1). Both TIV and LAIV are widely available in the United States. Although both types of vaccines are expected to be effective, the vaccines differ in several respects (Table 1).

Major Differences Between TIV and LAIV

During the preparation of TIV, the vaccine viruses are made noninfectious (i.e., inactivated or killed) (*103*). Only subvirion and purified surface antigen preparations of TIV (often referred to as "split" and subunit vaccines, respectively) are available in the United States. TIV contains killed viruses and thus cannot cause influenza. LAIV contains live, attenuated viruses that have the potential to cause mild signs or symptoms such as runny nose, nasal congestion, fever or sore throat. LAIV is administered intranasally by sprayer, whereas TIV is administered intramuscularly by injection. LAIV is licensed for

use among nonpregnant persons aged 2--49 years; safety has not been established in persons with underlying medical conditions that confer a higher risk of influenza complications. TIV is licensed for use among persons aged ≥6 months, including those who are healthy and those with chronic medical conditions (Table 1).

Correlates of Protection after Vaccination

Immune correlates of protection against influenza infection after vaccination include serum hemagglutination inhibition antibody and neutralizing antibody (*14,104*). Increased levels of antibody induced by vaccination decrease the risk for illness caused by strains that are antigenically similar to those strains of the same type or subtype included in the vaccine (*105--108*). The majority of healthy children and adults have high titers of antibody after vaccination (*106,109*). Although immune correlates such as achievement of certain antibody titers after vaccination correlate well with immunity on a population level, the significance of reaching or failing to reach a certain antibody threshold is not well understood on the individual level. Other immunologic correlates of protection that might best indicate clinical protection after receipt of an intranasal vaccine such as LAIV (e.g., mucosal antibody) are more difficult to measure (*103,110*).

Immunogenicity, Efficacy, and Effectiveness of TIV

Children

Children aged ≥6 months typically have protective levels of anti-influenza antibody against specific influenza virus strains after receiving the recommended number of doses of influenza vaccine (*104,109,111--116*). In most seasons, one or more vaccine antigens are changed compared to the previous season. In consecutive years when vaccine antigens change, children aged <9 years who received only 1 dose of vaccine in their first year of vaccination are less likely to have protective antibody responses when administered only a single dose during their second year of vaccination, compared with children who received 2 doses in their first year of vaccination (*117--119*).

When the vaccine antigens do not change from one season to the next, priming children aged 6--23 months with a single dose of vaccine in the spring followed by a dose in the fall engenders similar antibody responses compared with a regimen of 2 doses in the fall (*120*). However, one study conducted during a season when the vaccine antigens did not change compared with the previous season estimated 62% effectiveness against ILI for healthy children who had received only 1 dose in the previous influenza season and only 1 dose in the

study season, compared with 82% for those who received 2 doses separated by >4 weeks during the study season (*121*).

The antibody response among children at higher risk for influenza-related complications (e.g., children with chronic medical conditions) might be lower than those typically reported among healthy children (*122,123*). However, antibody responses among children with asthma are similar to those of healthy children and are not substantially altered during asthma exacerbations requiring short-term prednisone treatment (*124*).

Vaccine effectiveness studies also have indicated that 2 doses are needed to provide adequate protection during the first season that young children are vaccinated. Among children aged <5 years who have never received influenza vaccine previously or who received only 1 dose of influenza vaccine in their first year of vaccination, vaccine effectiveness is lower compared with children who receive 2 doses in their first year of being vaccinated. Two recent, large retrospective studies of young children who had received only 1 dose of TIV in their first year of being vaccinated determined that no decrease was observed in ILI-related office visits compared with unvaccinated children (*121,125*). Similar results were reported in a case-control study of children aged 6--59 months (*126*). These results, along with the immunogenicity data indicating that antibody responses are significantly higher when young children are given 2 doses, are the basis for the recommendation that all children aged <9 years who are being vaccinated for the first time should receive 2 vaccine doses separated by at least 4 weeks.

Certain studies have demonstrated vaccine efficacy or effectiveness among children aged ≥6 months, although estimates have varied. In a randomized trial conducted during five influenza seasons (1985--1990) in the United States among children aged 1--15 years, annual vaccination reduced laboratory-confirmed influenza A substantially (77%--91%) (*106*). A limited 1-year placebo-controlled study reported vaccine efficacy against laboratory-confirmed influenza illness of 56% among healthy children aged 3--9 years and 100% among healthy children and adolescents aged 10--18 years (*127*). A randomized, double-blind, placebo-controlled trial conducted during two influenza seasons among children aged 6--24 months indicated that efficacy was 66% against culture-confirmed influenza illness during 1999--2000, but did not significantly reduce culture-confirmed influenza illness during 2000--2001 (*128*). In a nonrandomized controlled trial among children aged 2--6 years and 7--14 years who had asthma, vaccine efficacy was 54% and 78% against laboratory-confirmed influenza type A infection and 22% and 60% against laboratory-confirmed influenza type B infection, respectively. Vaccinated children aged 2--6 years with asthma did not have substantially fewer type B influenza virus infections compared with the control group in this study (*129*).

Vaccination also might provide protection against asthma exacerbations (*130*); however, other studies of children with asthma have not demonstrated decreased exacerbations (*131*). Because of the recognized influenza-related disease burden among children with other chronic diseases or immunosuppression and the long-standing recommendation for vaccination of these children, randomized placebo-controlled studies to study efficacy in these children have not been conducted because of ethical considerations.

A retrospective study conducted among approximately 30,000 children aged 6 months--8 years during an influenza season (2003--04) with a suboptimal vaccine match indicated vaccine effectiveness of 51% against medically attended, clinically diagnosed pneumonia or influenza (i.e., no laboratory confirmation of influenza) among fully vaccinated children, and 49% among approximately 5,000 children aged 6--23 months (*125*). Another retrospective study of similar size conducted during the same influenza season in Denver but limited to healthy children aged 6--21 months estimated clinical effectiveness of 2 TIV doses to be 87% against pneumonia or influenza-related office visits (*121*). Among children, TIV effectiveness might increase with age (*106,132*).

TIV has been demonstrated to reduce acute otitis media in some studies. Two studies have reported that TIV decreases the risk for influenza-associated otitis media by approximately 30% among children with mean ages of 20 and 27 months, respectively (*133,134*). However, a large study conducted among children with a mean age of 14 months indicated that TIV was not effective against acute otitis media (*128*). Influenza vaccine effectiveness against acute otitis media, which is caused by a variety of pathogens and is not typically diagnosed using influenza virus culture, would be expected to be relatively low when assessing a nonspecific clinical outcome.

Adults Aged <65 Years

One dose of TIV is highly immunogenic in healthy adults aged <65 years. Limited or no increase in antibody response is reported among adults when a second dose is administered during the same season (*135--139*). When the vaccine and circulating viruses are antigenically similar, TIV prevents laboratory-confirmed influenza illness among approximately 70%--90% of healthy adults aged <65 years in randomized controlled trials (*139--142*). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched (*139--141,143--145*). Efficacy or effectiveness against laboratory-confirmed influenza illness was 50%--77% in studies conducted during different influenza seasons when the vaccine strains were antigenically dissimilar to the majority of circulating strains (*139,141,145--147*). However, effectiveness among healthy adults against

influenza-related hospitalization, measured in the most recent of these studies, was 90% (*147*).

In certain studies, persons with certain chronic diseases have lower serum antibody responses after vaccination compared with healthy young adults and can remain susceptible to influenza virus infection and influenza-related upper respiratory tract illness (*148*--*150*). Vaccine effectiveness among adults aged <65 years who are at higher risk for influenza complications is typically lower than that reported for healthy adults. In a case-control study conducted during 2003--2004, when the vaccine was a suboptimal antigenic match to many circulating virus strains, effectiveness for prevention of laboratory-confirmed influenza illness among adults aged 50--64 years with high risk conditions was 48%, compared with 60% for healthy adults (*147*). Effectiveness against hospitalization among adults aged 50--64 years with high-risk conditions was 36%, compared with 90% effectiveness among healthy adults in that age range (*147*). A randomized controlled trial among adults in Thailand with chronic obstructive pulmonary disease (median age: 68 years) indicated a vaccine effectiveness of 76% in preventing laboratory-confirmed influenza during a season when viruses were well-matched to vaccine viruses. Effectiveness did not decrease with increasing severity of underlying lung disease (*151*).

Studies using less specific outcomes, without laboratory confirmation of influenza virus infection, typically have demonstrated substantial reductions in hospitalizations or deaths among adults with risk factors for influenza complications. In a case-control study conducted in Denmark among adults with underlying medical conditions aged <65 years during 1999--2000, vaccination reduced deaths attributable to any cause 78% and reduced hospitalizations attributable to respiratory infections or cardiopulmonary diseases 87% (*152*). A benefit was reported after the first vaccination and increased with subsequent vaccinations in subsequent years (*153*). Among patients with diabetes mellitus, vaccination was associated with a 56% reduction in any complication, a 54% reduction in hospitalizations, and a 58% reduction in deaths (*154*). Certain experts have noted that the substantial effects on morbidity and mortality among those who received influenza vaccination in these observational studies should be interpreted with caution because of the difficulties in ensuring that those who received vaccination had similar baseline health status as those who did not (*101,102*). One meta-analysis of published studies did not determine sufficient evidence to conclude that persons with asthma benefit from vaccination (*155*). However, a meta-analysis that examined effectiveness among persons with chronic obstructive pulmonary disease identified evidence of benefit from vaccination (*156*).

Immunocompromised Persons

TIV produces adequate antibody concentrations against influenza among vaccinated HIV-infected persons who have minimal AIDS-related symptoms and normal or near-normal CD4+ T-lymphocyte cell counts (*157*--*159*). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, TIV might not induce protective antibody titers (*159,160*); a second dose of vaccine does not improve the immune response in these persons (*160,161*). A randomized, placebo-controlled trial determined that TIV was highly effective in preventing symptomatic, laboratory-confirmed influenza virus infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm3; however, a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study (*161*). A nonrandomized study of HIV-infected persons determined that influenza vaccination was most effective among persons with >100 CD4+ cells and among those with <30,000 viral copies of HIV type-1/mL (*77*).

On the basis of certain small studies, immunogenicity for persons with solid organ transplants varies according to transplant type. Among persons with kidney or heart transplants, the proportion who developed seroprotective antibody concentrations was similar or slightly reduced compared with healthy persons (*162*--*164*). However, a study among persons with liver transplants indicated reduced immunologic responses to influenza vaccination (*165*--*167*), especially if vaccination occurred within the 4 months after the transplant procedure (*165*).

Pregnant Women and Neonates

Pregnant women have protective levels of anti-influenza antibodies after vaccination (*168,169*). Passive transfer of anti-influenza antibodies that might provide protection from vaccinated women to neonates has been reported (*168,170*--*172*). A retrospective, clinic-based study conducted during 1998--2003 documented a nonsignificant trend towards fewer episodes of MAARI during one influenza season among vaccinated pregnant women compared with unvaccinated pregnant women and substantially fewer episodes of MAARI during the peak influenza season (*169*). However, a retrospective study conducted during 1997--2002 that used clinical records data did not indicate a reduction in ILI among vaccinated pregnant women or their infants (*173*). In another study conducted during 1995--2001, medical visits for respiratory illness among the infants were not substantially reduced (*174*). However, studies of influenza vaccine effectiveness among pregnant women have not included specific outcomes such as laboratory-confirmed influenza in women or their infants.

Older Adults

Adults aged ≥65 years typically have a diminished immune response to influenza vaccination compared with young healthy adults, suggesting that immunity might be of shorter duration (although still extending through one influenza season) (*175,176*). However, a review of the published literature concluded that no clear evidence existed that immunity declined more rapidly in the elderly (*177*). Infections among the vaccinated elderly might be associated with an age-related reduction in ability to respond to vaccination rather than reduced duration of immunity (*149--150*).

The only randomized controlled trial among community-dwelling persons aged ≥60 years reported a vaccine efficacy of 58% against influenza respiratory illness during a season when the vaccine strains were considered to be well-matched to circulating strains, but indicated that efficacy was lower among those aged ≥70 years (*178*). Influenza vaccine effectiveness in preventing MAARI among the elderly in nursing homes has been estimated at 20%--40% (*179,180*), and reported outbreaks among well-vaccinated nursing home populations have suggested that vaccination might not have any significant effectiveness when circulating strains are drifted from vaccine strains (*181,182*). In contrast, some studies have indicated that vaccination can be up to 80% effective in preventing influenza-related death (*179,183--185*). Among elderly persons not living in nursing homes or similar chronic-care facilities, influenza vaccine is 27%--70% effective in preventing hospitalization for pneumonia and influenza (*186--188*). Influenza vaccination reduces the frequency of secondary complications and reduces the risk for influenza-related hospitalization and death among community-dwelling adults aged ≥65 years with and without high-risk medical conditions (e.g., heart disease and diabetes) (*187--192*). However, studies demonstrating large reductions in hospitalizations and deaths among the vaccinated elderly have been conducted using medical record databases and have not measured reductions in laboratory-confirmed influenza illness. These studies have been challenged because of concerns that they have not adequately controlled for differences in the propensity for healthier persons to be more likely than less healthy persons to receive vaccination (*101,102,183,193--195*).

TIV Dosage, Administration, and Storage

The composition of TIV varies according to manufacturer, and package inserts should be consulted. TIV formulations in multidose vials contain the vaccine preservative thimerosal; preservative-free single dose preparations also are available. TIV should be stored at 35°F--46°F (2°C--8°C) and should not be frozen. TIV that has been frozen should be discarded. Dosage recommendations and schedules vary according to age group (Table 2). Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.

The intramuscular route is recommended for TIV. Adults and older children should be vaccinated in the deltoid muscle. A needle length of ≥1 inch (>25 mm) should be considered for persons in these age groups because needles of <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children (*196*). When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8--1.25 inches is recommended (*197*).

Infants and young children should be vaccinated in the anterolateral aspect of the thigh. A needle length of 7/8--1 inch should be used for children aged <12 months.

Adverse Events after Receipt of TIV

Children

Studies support the safety of annual TIV in children and adolescents. The largest published postlicensure population-based study assessed TIV safety in 215,600 children aged <18 years and 8,476 children aged 6--23 months enrolled in one of five health maintenance organizations (HMOs) during 1993--1999. This study indicated no increase in biologically plausible, medically attended events during the 2 weeks after inactivated influenza vaccination, compared with control periods 3--4 weeks before and after vaccination (*198*). A retrospective study using medical records data from approximately 45,000 children aged 6--23 months provided additional evidence supporting overall safety of TIV in this age group. Vaccination was not associated with statistically significant increases in any medically attended outcome, and 13 diagnoses, including acute upper respiratory illness, otitis media and asthma, were significantly less common (*199*).

In a study of 791 healthy children aged 1--15 years, postvaccination fever was noted among 11.5% of those aged 1--5 years, 4.6% among those aged 6--10 years, and 5.1% among those aged 11--15 years (*106*). Fever, malaise, myalgia, and other systemic symptoms that can occur after vaccination with inactivated vaccine most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) (*200,201*). These reactions begin 6--12 hours after vaccination and can persist for 1--2 days. Data about potential adverse events among children after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). A recently published review of VAERS reports submitted after administration of TIV to children aged 6--23 months documented that the most frequently reported adverse events were fever, rash, injection-site reactions, and seizures; the majority of the limited number of reported seizures appeared to be febrile (*202*). Because of the limitations of passive reporting systems, determining causality for specific types of adverse events, with the

exception of injection-site reactions, usually is not possible using VAERS data alone.

Adults

In placebo-controlled studies among adults, the most frequent side effect of vaccination was soreness at the vaccination site (affecting 10%--64% of patients) that lasted <2 days (*203,204*). These local reactions typically were mild and rarely interfered with the recipients' ability to conduct usual daily activities. Placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of TIV is not associated with higher rates for systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections (*139,155, 203--205*).

Pregnant Women and Neonates

FDA has classified TIV as a "Pregnancy Category C" medication, indicating that animal reproduction studies have not been conducted to support a labeling change. Available data indicate that influenza vaccine does not cause fetal harm when administered to a pregnant woman or affect reproductive capacity. One study of approximately 2,000 pregnant women who received TIV during pregnancy demonstrated no adverse fetal effects and no adverse effects during infancy or early childhood (*206*). A matched case-control study of 252 pregnant women who received TIV within the 6 months before delivery determined no adverse events after vaccination among pregnant women and no difference in pregnancy outcomes compared with 826 pregnant women who were not vaccinated (*169*). During 2000--2003, an estimated 2 million pregnant women were vaccinated, and only 20 adverse events among women who received TIV were reported to VAERS during this time, including nine injection-site reactions and eight systemic reactions (e.g., fever, headache, and myalgias). In addition, three miscarriages were reported, but these were not known to be causally related to vaccination (*207*). Similar results have been reported in certain smaller studies (*168,170,208*), and a recent international review of data on the safety of TIV concluded that no evidence exists to suggest harm to the fetus (*209*).

Persons with Chronic Medical Conditions

In a randomized cross-over study of children and adults with asthma, no increase in asthma exacerbations was reported for either age group (*210*), and a second study indicated no increase in wheezing among vaccinated asthmatic children (*130*). One study (*123*) reported that 20%--28% of children with asthma aged 9 months--18 years had local pain and swelling at the site of influenza vaccination, and another study (*113*) reported that 23% of children aged 6 months--4 years with chronic heart or lung disease had local reactions. A

blinded, randomized, cross-over study of 1,952 adults and children with asthma demonstrated that only self-reported "body aches" were reported more frequently after TIV (25%) than placebo-injection (21%) (*210*). However, a placebo-controlled trial of TIV indicated no difference in local reactions among 53 children aged 6 months--6 years with high-risk medical conditions or among 305 healthy children aged 3--12 years (*114*).

Among children with high-risk medical conditions, one study of 52 children aged 6 months--3 years reported fever among 27% and irritability and insomnia among 25% (*113*); and a study among 33 children aged 6--18 months reported that one child had irritability and one had a fever and seizure after vaccination (*211*). No placebo comparison group was used in these studies.

Immunocompromised Persons

Data demonstrating safety of TIV for HIV-infected persons are limited, but no evidence exists that vaccination has a clinically important impact on HIV infection or immunocompetence. One study demonstrated a transient (i.e., 2--4 week) increase in HIV RNA (ribonucleic acid) levels in one HIV-infected person after influenza virus infection (*212*). Studies have demonstrated a transient increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration (*159,213*). However, more recent and better-designed studies have not documented a substantial increase in the replication of HIV (*214--217*). CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated to change substantially after influenza vaccination among HIV-infected persons compared with unvaccinated HIV-infected persons (*159,218*). Limited information is available about the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza virus infection or influenza vaccination (*73,219*).

Data are similarly limited for persons with other immunocompromising conditions. In small studies, vaccination did not affect allograft function or cause rejection episodes in recipients of kidney transplants (*162,164*), heart transplants (*163*), or liver transplants (*165*).

Hypersensitivity

Immediate and presumably allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination (*220,221*). These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Manufacturers use a variety of different

compounds to inactivate influenza viruses and add antibiotics to prevent bacterial contamination. Package inserts should be consulted for additional information.

Persons who have had hives or swelling of the lips or tongue, or who have experienced acute respiratory distress or who collapse after eating eggs, should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma related to egg exposure or other allergic responses to egg protein, also might be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician before vaccination should be considered (*222--224*).

Hypersensitivity reactions to other vaccine components can occur but are rare. Although exposure to vaccines containing thimerosal can lead to hypersensitivity, the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity (*225,226*). When reported, hypersensitivity to thimerosal typically has consisted of local delayed hypersensitivity reactions (*225*).

Guillain-Barré Syndrome and TIV

The annual incidence of Guillain-Barré Syndrome (GBS) is 10--20 cases per 1 million adults (*227*). Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, are associated with GBS (*228--230*). The 1976 swine influenza vaccine was associated with an increased frequency of GBS (*231,232*), estimated at one additional case of GBS per 100,000 persons vaccinated. The risk for influenza vaccine-associated GBS was higher among persons aged ≥25 years than among persons aged <25 years (*233*). However, obtaining strong epidemiologic evidence for a possible small increase in risk for a rare condition with multiple causes is difficult, and no evidence exists for a consistent causal relation between subsequent vaccines prepared from other influenza viruses and GBS.

None of the studies conducted using influenza vaccines other than the 1976 swine influenza vaccine have demonstrated a substantial increase in GBS associated with influenza vaccines. During three of four influenza seasons studied during 1977--1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant in any of these studies (*234--236*). However, in a study of the 1992--93 and 1993--94 seasons, the overall relative risk for GBS was 1.7 (CI = 1.0--2.8; p = 0.04) during the 6 weeks after vaccination, representing approximately one additional case of GBS per 1

million persons vaccinated; the combined number of GBS cases peaked 2 weeks after vaccination (*231*). Results of a study that examined health-care data from Ontario, Canada, during 1992--2004 demonstrated a small but statistically significant temporal association between receiving influenza vaccination and subsequent hospital admission for GBS. However, no increase in cases of GBS at the population level was reported after introduction of a mass public influenza vaccination program in Ontario beginning in 2000 (*237*). Data from VAERS have documented decreased reporting of GBS occurring after vaccination across age groups over time, despite overall increased reporting of other, non-GBS conditions occurring after administration of influenza vaccine (*203*). Cases of GBS after influenza virus infection have been reported, but no other epidemiologic studies have documented such an association (*238,239*). Recently published data from the United Kingdom's General Practice Research Database (GPRD) found influenza vaccine to be protective against GBS, although it is unclear if this was associated with protection against influenza or confounding because of a "healthy vaccinee" (e.g., healthier persons might be more likely to be vaccinated and are lower risk for GBS) (*240*). A separate GPRD analysis found no association between vaccination and GBS over a 9 year period; only three cases of GBS occurred within 6 weeks after influenza vaccine (*241*).

If GBS is a side effect of influenza vaccines other than 1976 swine influenza vaccine, the estimated risk for GBS (on the basis of the few studies that have demonstrated an association between vaccination and GBS) is low (i.e., approximately one additional case per 1 million persons vaccinated). The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh these estimates of risk for vaccine-associated GBS. No evidence indicates that the case fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

Use of TIV among Patients with a History of GBS

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (*227*). Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown. However, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination might be prudent as a precaution. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, the established

benefits of influenza vaccination might outweigh the risks for many persons who have a history of GBS and who are also at high risk for severe complications from influenza.

Vaccine Preservative (Thimerosal) in Multidose Vials of TIV

Thimerosal, a mercury-containing anti-bacterial compound, has been used as a preservative in vaccines since the 1930s (*242*) and is used in multidose vial preparations of TIV to reduce the likelihood of bacterial contamination. No scientific evidence indicates that thimerosal in vaccines, including influenza vaccines, is a cause of adverse events other than occasion local hypersensitivity reactions in vaccine recipients. In addition, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received vaccine during pregnancy. Evidence is accumulating that supports the absence of substantial risk for neurodevelopment disorders or other harm resulting from exposure to thimerosal-containing vaccines (*243--250*). However, continuing public concern about exposure to mercury in vaccines was viewed as a potential barrier to achieving higher vaccine coverage levels and reducing the burden of vaccine-preventable diseases. Therefore, the U.S. Public Health Service and other organizations recommended that efforts be made to eliminate or reduce the thimerosal content in vaccines as part of a strategy to reduce mercury exposures from all sources (*243,245,247*). Since mid-2001, vaccines routinely recommended for infants aged <6 months in the United States have been manufactured either without or with greatly reduced (trace) amounts of thimerosal. As a result, a substantial reduction in the total mercury exposure from vaccines for infants and children already has been achieved (*197*). ACIP and other federal agencies and professional medical organizations continue to support efforts to provide thimerosal preservative--free vaccine options.

The benefits of influenza vaccination for all recommended groups, including pregnant women and young children, outweigh concerns on the basis of a theoretical risk from thimerosal exposure through vaccination. The risks for severe illness from influenza virus infection are elevated among both young children and pregnant women, and vaccination has been demonstrated to reduce the risk for severe influenza illness and subsequent medical complications. In contrast, no scientifically conclusive evidence has demonstrated harm from exposure to vaccine containing thimerosal preservative. For these reasons, persons recommended to receive TIV may receive any age- and risk factor--appropriate vaccine preparation, depending on availability. An analysis of VAERS reports found no difference in the safety profile of preservative-containing compared with preservative-free TIV vaccines in infants aged 6--23 months (*202*).

Nonetheless, certain states have enacted legislation banning the administration of vaccines containing mercury; the provisions defining mercury content vary (*251*). LAIV and many of the single dose vial or syringe preparations of TIV are thimerosal-free, and the number of influenza vaccine doses that do not contain thimerosal as a preservative is expected to increase (Table 2). However, these laws might present a barrier to vaccination unless influenza vaccines that do not contain thimerosal as a preservative are easily available in those states.

The U.S. vaccine supply for infants and pregnant women is in a period of transition during which the availability of thimerosal-reduced or thimerosal-free vaccine intended for these groups is being expanded by manufacturers as a feasible means of further reducing an infant's cumulative exposure to mercury. Other environmental sources of mercury exposure are more difficult or impossible to avoid or eliminate (*243*).

LAIV Dosage, Administration, and Storage

Each dose of LAIV contains the same three vaccine antigens used in TIV. However, the antigens are constituted as live, attenuated, cold-adapted, temperature-sensitive vaccine viruses. Additional components of LAIV include egg allantoic fluid, monosodium glutamate, sucrose, phosphate, and glutamate buffer; and hydrolyzed porcine gelatin. LAIV does not contain thimerosal. LAIV is made from attenuated viruses that are only able to replicate efficiently at temperatures present in the nasal mucosa. LAIV does not cause systemic symptoms of influenza in vaccine recipients, although a minority of recipients experience nasal congestion, which is probably a result of either effects of intranasal vaccine administration or local viral replication or fever (*252*).

LAIV is intended for intranasal administration only and should not be administered by the intramuscular, intradermal, or intravenous route. LAIV is not licensed for vaccination of children aged <2 years or adults aged >49 years. LAIV is supplied in a prefilled, single-use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. LAIV is shipped to end users at 35°F--46°F (2°C--8°C). LAIV should be stored at 35°F--46°F (2°C--8°C) on receipt and can remain at that temperature until the expiration date is reached (*252*). Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.

Shedding, Transmission, and Stability of Vaccine Viruses

Available data indicate that both children and adults vaccinated with LAIV can shed vaccine viruses after vaccination, although in lower amounts than occur

typically with shedding of wild-type influenza viruses. In rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. However, serious illnesses have not been reported among unvaccinated persons who have been infected inadvertently with vaccine viruses.

One study of children aged 8--36 months in a child care center assessed transmissibility of vaccine viruses from 98 vaccinated to 99 unvaccinated subjects; 80% of vaccine recipients shed one or more virus strains (mean duration: 7.6 days). One influenza type B vaccine strain isolate was recovered from a placebo recipient and was confirmed to be vaccine-type virus. The type B isolate retained the cold-adapted, temperature-sensitive, attenuated phenotype, and it possessed the same genetic sequence as a virus shed from a vaccine recipient who was in the same play group. The placebo recipient from whom the influenza type B vaccine strain was isolated had symptoms of a mild upper respiratory illness but did not experience any serious clinical events. The estimated probability of acquiring vaccine virus after close contact with a single LAIV recipient in this child care population was 0.6%--2.4% (*253*).

Studies assessing whether vaccine viruses are shed have been based on viral cultures or PCR detection of vaccine viruses in nasal aspirates from persons who have received LAIV. One study of 20 healthy vaccinated adults aged 18--49 years demonstrated that the majority of shedding occurred within the first 3 days after vaccination, although the vaccine virus was detected in one subject on day 7 after vaccine receipt. Duration or type of symptoms associated with receipt of LAIV did not correlate with detection of vaccine viruses in nasal aspirates (*254*). Another study in 14 healthy adults aged 18--49 years indicated that 50% of these adults had viral antigen detected by direct immunofluorescence or rapid antigen tests within 7 days of vaccination. The majority of samples with detectable virus were collected on day 2 or 3 (*255*). Vaccine strain virus was detected from nasal secretions in one (2%) of 57 HIV-infected adults who received LAIV, none of 54 HIV-negative participants (*256*), and three (13%) of 23 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (*257*). No participants in these studies had detectable virus beyond 10 days after receipt of LAIV. The possibility of person-to-person transmission of vaccine viruses was not assessed in these studies (*254*--*257*).

In clinical trials, viruses isolated from vaccine recipients have been phenotypically stable. In one study, nasal and throat swab specimens were collected from 17 study participants for 2 weeks after vaccine receipt (*258*). Virus isolates were analyzed by multiple genetic techniques. All isolates retained the LAIV genotype after replication in the human host, and all retained the cold-adapted and temperature-sensitive phenotypes. A study conducted in a

child-care setting demonstrated that limited genetic change occurred in the LAIV strains following replication in the vaccine recipients (*259*).

Immunogenicity, Efficacy, and Effectiveness of LAIV

LAIV virus strains replicate primarily in nasopharyngeal epithelial cells. The protective mechanisms induced by vaccination with LAIV are not understood completely but appear to involve both serum and nasal secretory antibodies. The immunogenicity of the approved LAIV has been assessed in multiple studies conducted among children and adults (*106,260--266*). No single laboratory measurement closely correlates with protective immunity induced by LAIV (*261*).

Healthy Children

A randomized, double-blind, placebo-controlled trial among 1,602 healthy children aged 15--71 months assessed the efficacy of LAIV against culture-confirmed influenza during two seasons (*267,268*). This trial included a subset of children aged 60--71 months who received 2 doses in the first season. In season one (1996--97), when vaccine and circulating virus strains were well-matched, efficacy against culture-confirmed influenza was 94% for participants who received 2 doses of LAIV separated by ≥6 weeks, and 89% for those who received 1 dose. In season two, when the A (H3N2) component in the vaccine was not well-matched with circulating virus strains, efficacy (1 dose) was 86%, for an overall efficacy over two influenza seasons of 92%. Receipt of LAIV also resulted in 21% fewer febrile illnesses and a significant decrease in acute otitis media requiring antibiotics (*267,269*). Other randomized, placebo-controlled trials demonstrating the efficacy of LAIV in young children against culture-confirmed influenza include a study conducted among children aged 6--35 months attending child care centers during consecutive influenza seasons (*270*), in which 85%--89% efficacy was observed, and a study conducted among children aged 12--36 months living in Asia during consecutive influenza seasons, in which 64%-70% efficacy was documented (*271*). In one community-based, nonrandomized open-label study, reductions in MAARI were observed among children who received 1 dose of LAIV during the 1990--00 and 2000--01 influenza seasons even though antigenically drifted influenza A/H1N1 and B viruses were circulating during that season (*272*). LAIV efficacy in preventing laboratory confirmed influenza has also been demonstrated in studies comparing the efficacy of LAIV with TIV rather than with a placebo (see Comparisons of LAIV and TIV Efficacy or Effectiveness).

Healthy Adults

A randomized, double-blind, placebo-controlled trial of LAIV effectiveness among 4,561 healthy working adults aged 18--64 years assessed multiple

endpoints, including reductions in self-reported respiratory tract illness without laboratory confirmation, work loss, health-care visits, and medication use during influenza outbreak periods (*273*). The study was conducted during the 1997--98 influenza season, when the vaccine and circulating A (H3N2) strains were not well-matched. The frequency of febrile illnesses was not significantly decreased among LAIV recipients compared with those who received placebo. However, vaccine recipients had significantly fewer severe febrile illnesses (19% reduction) and febrile upper respiratory tract illnesses (24% reduction), and significant reductions in days of illness, days of work lost, days with health-care--provider visits, and use of prescription antibiotics and over-the-counter medications (*273*). Efficacy against culture-confirmed influenza in a randomized, placebo-controlled study was 57%, although efficacy in this study was not demonstrated to be significantly greater than placebo (*155*).

Adverse Events after Receipt of LAIV

Healthy Children Aged 2--18 Years

In a subset of healthy children aged 60--71 months from one clinical trial (*233*), certain signs and symptoms were reported more often after the first dose among LAIV recipients (n = 214) than among placebo recipients (n = 95), including runny nose (48% and 44%, respectively); headache (18% and 12%, respectively); vomiting (5% and 3%, respectively); and myalgias (6% and 4%, respectively). However, these differences were not statistically significant. In other trials, signs and symptoms reported after LAIV administration have included runny nose or nasal congestion (20%--75%), headache (2%--46%), fever (0--26%), vomiting (3%--13%), abdominal pain (2%), and myalgias (0--21%) (*106,260,263, 265,270,273--276*). These symptoms were associated more often with the first dose and were self-limited.

In a randomized trial published in 2007, LAIV and TIV were compared among children aged 6--59 months (*277*). Children with medically diagnosed or treated wheezing within 42 days before enrollment, or a history of severe asthma, were excluded from this study. Among children aged 24--59 months who received LAIV, the rate of medically significant wheezing, using a pre-specified definition, was not greater compared with those who received TIV (*277*); wheezing was observed more frequently among younger LAIV recipients in this study (see Persons at Higher Risk from Influenza-Related Complications). In a previous randomized placebo-controlled safety trial among children aged 12 months--17 years without a history of asthma by parental report, an elevated risk for asthma events (RR = 4.06, CI = 1.29--17.86) was documented among 728 children aged 18--35 months who received LAIV. Of the 16 children with asthma-related events in this study, seven had a history of asthma on the basis of subsequent

medical record review. None required hospitalization, and elevated risks for asthma were not observed in other age groups (*276*).

Another study was conducted among >11,000 children aged 18 months--18 years in which 18,780 doses of vaccine were administered for 4 years. For children aged 18 months--4 years, no increase was reported in asthma visits 0--15 days after vaccination compared with the prevaccination period. A significant increase in asthma events was reported 15--42 days after vaccination, but only in vaccine year 1 (*278*).

Initial data from VAERS during 2007--2008, following ACIP recommendation for LAIV use in children aged 2--4 years, do not suggest a concern for wheezing after LAIV in young children. However data also suggest uptake of LAIV is limited and continued safety monitoring for wheezing events after LAIV is indicated (CDC, unpublished data, 2008).

Adults Aged 19--49 Years

Among adults, runny nose or nasal congestion (28%--78%), headache (16%--44%), and sore throat (15%--27%) have been reported more often among vaccine recipients than placebo recipients (*252,279*). In one clinical trial among a subset of healthy adults aged 18--49 years, signs and symptoms reported more frequently among LAIV recipients (n = 2,548) than placebo recipients (n = 1,290) within 7 days after each dose included cough (14% and 11%, respectively); runny nose (45% and 27%, respectively); sore throat (28% and 17%, respectively); chills (9% and 6%, respectively); and tiredness/weakness (26% and 22%, respectively) (*279*).

Persons at Higher Risk for Influenza-Related Complications

Limited data assessing the safety of LAIV use for certain groups at higher risk for influenza-related complications are available. In one study of 54 HIV-infected persons aged 18--58 years and with CD4 counts ≥200 cells/mm3 who received LAIV, no serious adverse events were reported during a 1-month follow-up period (*256*). Similarly, one study demonstrated no significant difference in the frequency of adverse events or viral shedding among HIV-infected children aged 1--8 years on effective antiretroviral therapy who were administered LAIV, compared with HIV-uninfected children receiving LAIV (*257*). LAIV was well-tolerated among adults aged ≥65 years with chronic medical conditions (*280*). These findings suggest that persons at risk for influenza complications who have inadvertent exposure to LAIV would not have significant adverse events or prolonged viral shedding and that persons who have contact with persons at higher risk for influenza-related complications may receive LAIV.

Serious Adverse Events

Serious adverse events after administration of LAIV requiring medical attention among healthy children aged 5--17 years or healthy adults aged 18--49 years occurred at a rate of <1% (*252*). Surveillance will continue for adverse events, including those that might not have been detected in previous studies. Reviews of reports to VAERS after vaccination of approximately 2.5 million persons during the 2003--04 and 2004--05 influenza seasons did not indicate any new safety concerns (*281*). Health-care professionals should report all clinically significant adverse events occurring after LAIV administration promptly to VAERS after LAIV administration.

Comparisons of LAIV and TIV Efficacy or Effectiveness

Both TIV and LAIV have been demonstrated to be effective in children and adults, but data directly comparing the efficacy or effectiveness of these two types of influenza vaccines are limited. Studies comparing the efficacy of TIV to that of LAIV have been conducted in a variety of settings and populations using several different outcomes. One randomized, double-blind, placebo-controlled challenge study among 92 healthy adults aged 18--41 years assessed the efficacy of both LAIV and TIV in preventing influenza infection when challenged with wild-type strains that were antigenically similar to vaccine strains (*282*). The overall efficacy in preventing laboratory-documented influenza from all three influenza strains combined was 85% and 71%, respectively, when challenged 28 days after vaccination by viruses to which study participants were susceptible before vaccination. The difference in efficacy between the two vaccines was not statistically significant in this limited study. No additional challenges to assess efficacy at time points later than 28 days were conducted. In a randomized, double-blind, placebo-controlled trial, conducted among young adults during an influenza season when the majority of circulating H3N2 viruses were antigenically drifted from that season's vaccine viruses, the efficacy of LAIV and TIV against culture-confirmed influenza was 57% and 77%, respectively. The difference in efficacy was not statistically significant and was based largely on a difference in efficacy against influenza B (*155*).

A randomized controlled clinical trial conducted among children aged 6--71 months during the 2004--05 influenza season demonstrated a 55% reduction in cases of culture-confirmed influenza among children who received LAIV compared with those who received TIV (*277*). In this study, LAIV efficacy was higher compared with TIV against antigenically drifted viruses as well as well-matched viruses (*277*). An open-label, nonrandomized, community-based influenza vaccine trial conducted during an influenza season when circulating H3N2 strains were poorly matched with strains contained in the vaccine also indicated that LAIV, but not TIV, was effective against antigenically drifted H3N2 strains during that influenza season. In this study, children aged 5--18 years

who received LAIV had significant protection against laboratory-confirmed influenza (37%) and pneumonia and influenza events (50%) (*278*).

Although LAIV is not licensed for use in persons with risk factors for influenza complications, certain studies have compared the efficacy of LAIV to TIV in these groups. LAIV provided 32% increased protection in preventing culture-confirmed influenza compared with TIV in one study conducted among children aged ≥6 years and adolescents with asthma (*283*) and 52% increased protection compared with TIV among children aged 6--71 months with recurrent respiratory tract infections (*284*).

Effectiveness of Vaccination for Decreasing Transmission to Contacts

Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce ILI and complications among persons at high risk. Influenza virus infection and ILI are common among HCP (*285*--*287*). Influenza outbreaks have been attributed to low vaccination rates among HCP in hospitals and long-term--care facilities (*288*--*290*). One serosurvey demonstrated that 23% of HCP had serologic evidence of influenza virus infection during a single influenza season; the majority had mild illness or subclinical infection (*285*). Observational studies have demonstrated that vaccination of HCP is associated with decreased deaths among nursing home patients (*291,292*). In one cluster-randomized controlled trial that included 2,604 residents of 44 nursing homes, significant decreases in mortality, ILI, and medical visits for ILI care were demonstrated among residents in nursing homes in which staff were offered influenza vaccination (coverage rate: 48%), compared with nursing homes in which staff were not provided with vaccination (coverage rate: 6%) (*293*). A review concluded that vaccination of HCP in settings in which patients were also vaccinated provided significant reductions in deaths among elderly patients from all causes and deaths from pneumonia (*294*).

Epidemiologic studies of community outbreaks of influenza demonstrate that school-age children typically have the highest influenza illness attack rates, suggesting routine universal vaccination of children might reduce transmission to their household contacts and possibly others in the community. Results from certain studies have indicated that the benefits of vaccinating children might extend to protection of their adult contacts and to persons at risk for influenza complications in the community. However, these data are limited and studies have not used laboratory-confirmed influenza as an outcome measure. A single-blinded, randomized controlled study conducted during as part of a 1996--1997 vaccine effectiveness study demonstrated that vaccinating preschool-aged children with TIV reduced influenza-related morbidity among some household contacts (*295*). A randomized, placebo-controlled trial among

children with recurrent respiratory tract infections demonstrated that members of families with children who had received LAIV were significantly less likely to have respiratory tract infections and reported significantly fewer workdays lost, compared with families with children who received placebo (*296*). In nonrandomized community-based studies, administration of LAIV has been demonstrated to reduce MAARI (*297,298*) and ILI-related economic and medical consequences (e.g., workdays lost and number of health-care provider visits) among contacts of vaccine recipients (*298*). Households with children attending schools in which school-based LAIV vaccination programs had been established reported less ILI and fewer physician visits during peak influenza season, compared with households with children in schools in which no LAIV vaccination had been offered. However a decrease in the overall rate of school absenteeism was not reported in communities in which LAIV vaccination was offered (*298*). These community-based studies have not used laboratory-confirmed influenza as an outcome.

Some studies have also documented reductions in influenza illness among persons living in communities where focused programs for vaccinating children have been conducted. A community-based observational study conducted during the 1968 pandemic using a univalent inactivated vaccine reported that a vaccination program targeting school-aged children (coverage rate: 86%) in one community reduced influenza rates within the community among all age groups compared with another community in which aggressive vaccination was not conducted among school-aged children (*299*). An observational study conducted in Russia demonstrated reductions in ILI among the community-dwelling elderly after implementation of a vaccination program using TIV for children aged 3--6 years (57% coverage achieved) and children and adolescents aged 7--17 years (72% coverage achieved) (*300*). In a nonrandomized community-based study conducted over three influenza seasons, 8%--18% reductions in the incidence of MAARI during the influenza season among adults aged ≥35 years were observed in communities in which LAIV was offered to all children aged ≥18 months (estimated coverage rate: 20%--25%) compared with communities with such vaccination programs (*297*). In a subsequent influenza season, the same investigators documented a 9% reduction in MAARI rates during the influenza season among persons aged 35--44 years in intervention communities, where coverage was estimated at 31% among school children, compared with control communities. However, MAARI rates among persons aged ≥45 years were lower in the intervention communities regardless of the presence of influenza in the community, suggesting that lower rates could not be attributed to vaccination of school children against influenza (*301*).

Effectiveness of Influenza Vaccination when Circulating Influenza Virus Strains Differ from Vaccine Strains

Manufacturing trivalent influenza virus vaccines is a challenging process that takes 6--8 months to complete. This manufacturing timeframe requires that influenza vaccine strains for influenza vaccines used in the United States must be selected in February of each year by the FDA to allow time for manufacturers to prepare vaccines for the next influenza season. Vaccine strain selections are based on global viral surveillance data that is used to identify trends in antigenic changes among circulating influenza viruses and the availability of suitable vaccine virus candidates.

Vaccination can provide reduced but substantial cross-protection against drifted strains in some seasons, including reductions in severe outcomes such as hospitalization. Usually one or more circulating viruses with antigenic changes compared with the vaccine strains are identified in each influenza season. However, assessment of the clinical effectiveness of influenza vaccines cannot be determined solely by laboratory evaluation of the degree of antigenic match between vaccine and circulating strains. In some influenza seasons, circulating influenza viruses with significant antigenic differences predominate and, compared with seasons when vaccine and circulating strains are well-matched, reductions in vaccine effectiveness are sometimes observed (*126,139,145, 147,191*). However, even during years when vaccine strains were not antigenically well matched to circulating strains, substantial protection has been observed against severe outcomes, presumably because of vaccine-induced cross-reacting antibodies (*139,145,147,273*). For example, in one study conducted during an influenza season (2003--04) when the predominant circulating strain was an influenza A (H3N2) virus that was antigenically different from that season's vaccine strain, effectiveness among persons aged 50--64 years against laboratory-confirmed influenza illness was 60% among healthy persons and 48% among persons with medical conditions that increase risk for influenza complications (*147*). An interim, within-season analysis during the 2007--08 influenza season indicated that vaccine effectiveness was 44% overall, 54% among healthy persons aged 5--49 years, and 58% against influenza A, despite the finding that viruses circulating in the study area were predominately a drifted influenza A H3N2 and a influenza B strain from a different lineage compared with vaccine strains (*302*). Among children, both TIV and LAIV provide protection against infection even in seasons when vaccines and circulating strains are not well matched. Vaccine effectiveness against ILI was 49%--69% in two observational studies, and 49% against medically attended, laboratory-confirmed influenza in a case-control study conducted among young children during the 2003--04 influenza season, when a drifted influenza A H3N2 strain predominated, based on viral surveillance data (*121,125*). However, continued improvements in collecting representative circulating viruses and use surveillance data to forecast antigenic drift are needed. Shortening manufacturing time to increase the time to identify good vaccine candidate strains from among the most recent circulating strains also is

important. Data from multiple seasons and collected in a consistent manner are needed to better understand vaccine effectiveness during seasons when circulating and vaccine virus strains are not well-matched.

Cost-Effectiveness of Influenza Vaccination

Economic studies of influenza vaccination are difficult to compare because they have used different measures of both costs and benefits (e.g., cost-only, cost-effectiveness, cost-benefit, or cost-utility). However, most studies find that vaccination reduces or minimizes health care, societal, and individual costs, or the productivity losses and absenteeism associated with influenza illness. One national study estimated the annual economic burden of seasonal influenza in the United States (using 2003 population and dollars) to be $87.1 billion, including $10.4 billion in direct medical costs (*303*).

Studies of influenza vaccination in the United States among persons aged ≥65 years have documented substantial reductions in hospitalizations and deaths and overall societal cost savings (*186,187*). Studies comparing adults in different age groups also find that vaccination is economically beneficial. One study that compared the economic impact of vaccination among persons aged ≥65 years with those aged 15--64 years indicated that vaccination resulted in a net savings per quality-adjusted life year (QALY) and that the Medicare program saved costs of treating illness by paying for vaccination (*304*). A study of a larger population comparing persons aged 50--64 years with those aged ≥65 years estimated the cost-effectiveness of influenza vaccination to be $28,000 per QALY saved (in 2000 dollars) in persons aged 50--64 years compared with $980 per QALY saved among persons aged ≥65 years (*305*).

Economic analyses among adults aged <65 years have reported mixed results regarding influenza vaccination. Two studies in the United States found that vaccination can reduce both direct medical costs and indirect costs from work absenteeism and reduced productivity (*306,307*). However, another United States study indicated no productivity and absentee savings in a strategy to vaccinate healthy working adults, although vaccination was still estimated to be cost-effective (*139*).

Cost analyses have documented the considerable cost burden of illness among children. In a study of 727 children at a medical center during 2000--2004, the mean total cost of hospitalization for influenza-related illness was $13,159 ($39,792 for patients admitted to an intensive care unit and $7,030 for patients cared for exclusively on the wards) (*308*). Strategies that focus on vaccinating children with medical conditions that confer a higher risk for influenza complications are more cost-effective than a strategy of vaccinating all children (*309*). An analysis that compared the costs of vaccinating children of varying ages with TIV and LAIV indicated that costs per QALY saved increased with

age for both vaccines. In 2003 dollars per QALY saved, costs for routine vaccination using TIV were $12,000 for healthy children aged 6--23 months and $119,000 for healthy adolescents aged 12--17 years, compared with $9,000 and $109,000 using LAIV, respectively (*310*). Economic evaluations of vaccinating children have demonstrated a wide range of cost estimates, but have generally found this strategy to be either cost-saving or cost-beneficial (*311--314*).

Economic analyses are sensitive to the vaccination venue, with vaccination in medical care settings incurring higher projected costs. In a published model, the mean cost (year 2004 values) of vaccination was lower in mass vaccination ($17.04) and pharmacy ($11.57) settings than in scheduled doctor's office visits ($28.67) (*315*). Vaccination in nonmedical settings was projected to be cost saving for healthy adults aged ≥50 years and for high-risk adults of all ages. For healthy adults aged 18--49 years, preventing an episode of influenza would cost $90 if vaccination were delivered in a pharmacy setting, $210 in a mass vaccination setting, and $870 during a scheduled doctor's office visit (*315*). Medicare payment rates in recent years have been less than the costs associated with providing vaccination in a medical practice (*316*).

Vaccination Coverage Levels

Continued annual monitoring is needed to determine the effects on vaccination coverage of vaccine supply delays and shortages, changes in influenza vaccination recommendations and target groups for vaccination, reimbursement rates for vaccine and vaccine administration, and other factors related to vaccination coverage among adults and children. One of the national health objectives for 2010 includes achieving an influenza vaccination coverage level of 90% for persons aged ≥65 years and among nursing home residents (*317,318*); new strategies to improve coverage are needed to achieve these objectives (*319,320*). Increasing vaccination coverage among persons who have high-risk conditions and are aged <65 years, including children at high risk, is the highest priority for expanding influenza vaccine use.

On the basis of the 2006 final data set and the 2007 early release data from the National Health Interview Survey (NHIS), estimated national influenza vaccine coverage during the 2005--06 and 2006--07 influenza seasons among persons aged ≥65 years and 50--64 years increased slightly from 32% and 65%, respectively to 36% and 66% (Table 3) and appear to be approaching coverage levels observed before the 2004--05 vaccine shortage year. In 2005--06 and 2006--07, estimated vaccination coverage levels among adults with high-risk conditions aged 18--49 years were 23% and 26%, respectively, substantially lower than the *Healthy People 2000* and *Healthy People 2010* objectives of 60% (Table 3) (*317,318*).

Opportunities to vaccinate persons at risk for influenza complications (e.g., during hospitalizations for other causes) often are missed. In a study of hospitalized Medicare patients, only 31.6% were vaccinated before admission, 1.9% during admission, and 10.6% after admission (*321*). A study in New York City during 2001--2005 among 7,063 children aged 6--23 months indicated that 2-dose vaccine coverage increased from 1.6% to 23.7%. Although the average number of medical visits during which an opportunity to be vaccinated decreased during the course of the study from 2.9 to 2.0 per child, 55% of all visits during the final year of the study still represented a missed vaccination opportunity (*322*). Using standing orders in hospitals increases vaccination rates among hospitalized persons (*323*). In one survey, the strongest predictor of receiving vaccination was the survey respondent's belief that he or she was in a high-risk group. However, many persons in high-risk groups did not know that they were in a group recommended for vaccination (*324*).

Reducing racial and ethnic health disparities, including disparities in influenza vaccination coverage, is an overarching national goal that is not being met (*317*). Estimated vaccination coverage levels in 2007 among persons aged ≥65 years were 70% for non-Hispanic whites, 58% for non-Hispanic blacks, and 54% for Hispanics (*325*). Among Medicare beneficiaries, other key factors that contribute to disparities in coverage include variations in the propensity of patients to actively seek vaccination and variations in the likelihood that providers recommend vaccination (*326,327*). One study estimated that eliminating these disparities in vaccination coverage would have an impact on mortality similar to the impact of eliminating deaths attributable to kidney disease among blacks or liver disease among Hispanics (*328*).

Reported vaccination levels are low among children at increased risk for influenza complications. Coverage among children aged 2--17 years with asthma for the 2004--05 influenza season was estimated to be 29% (*329*). One study reported 79% vaccination coverage among children attending a cystic fibrosis treatment center (*330*). During the first season for which ACIP recommended that all children aged 6 months--23 months receive vaccination, 33% received one or more dose of influenza vaccination, and 18% received 2 doses if they were unvaccinated previously (*331*). Among children enrolled in HMOs who had received a first dose during 2001--2004, second dose coverage varied from 29% to 44% among children aged 6--23 months and from 12% to 24% among children aged 2--8 years (*332*). A rapid analysis of influenza vaccination coverage levels among members of an HMO in Northern California demonstrated that during 2004--2005, the first year of the recommendation for vaccination of children aged 6--23 months, 1-dose coverage was 57% (*333*). During the 2005--06 influenza season, the second season for which ACIP recommended that all children aged 6 months--23 months receive vaccination, coverage remained low and did not increase substantially from the 2004--05

season. Data collected in 2006 by the National Immunization Survey indicated that for the 2005--06 season, 32% of children aged 6--23 months received at least 1 dose of influenza vaccine and 21% were fully vaccinated (i.e., received 1 or 2 doses depending on previous vaccination history); however, results varied substantially among states (*334*). As has been reported for older adults, a physician recommendation for vaccination and the perception that having a child be vaccinated "is a smart idea" were associated positively with likelihood of vaccination of children aged 6--23 months (*335*). Similarly, children with asthma were more likely to be vaccinated if their parents recalled a physician recommendation to be vaccinated or believed that the vaccine worked well (*336*). Implementation of a reminder/recall system in a pediatric clinic increased the percentage of children with asthma or reactive airways disease receiving vaccination from 5% to 32% (*337*).

Although annual vaccination is recommended for HCP and is a high priority for reducing morbidity associated with influenza in health-care settings and for expanding influenza vaccine use (*338*--*340*), national survey data demonstrated a vaccination coverage level of only 42% among HCP during the 2005--06 season (Table 3). Vaccination of HCP has been associated with reduced work absenteeism (*286*) and with fewer deaths among nursing home patients (*292,293*) and elderly hospitalized patients (*294*). Factors associated with a higher rate of influenza vaccination among HCP include older age, being a hospital employee, having employer provided health-care insurance, having had pneumococcal or hepatitis B vaccination in the past, or having visited a health-care professional during the preceding year. Non-Hispanic black HCP were less likely than non-Hispanic white HCP to be vaccinated (*341*). Beliefs that are frequently cited by HCP who decline vaccination include doubts about the risk for influenza and the need for vaccination, concerns about vaccine effectiveness and side effects, and dislike of injections (*342*).

Vaccine coverage among pregnant women has not increased significantly during the preceding decade. (*343*). Only 12% and 13% of pregnant women participating in the 2006 and 2007 NHIS reported vaccination during the 2005--06 and 2006--07 seasons, respectively, excluding pregnant women who reported diabetes, heart disease, lung disease, and other selected high-risk conditions (Table 3). In a study of influenza vaccine acceptance by pregnant women, 71% of those who were offered the vaccine chose to be vaccinated (*344*). However, a 1999 survey of obstetricians and gynecologists determined that only 39% administered influenza vaccine to obstetric patients in their practices, although 86% agreed that pregnant women's risk for influenza-related morbidity and mortality increases during the last two trimesters (*345*).

Influenza vaccination coverage in all groups recommended for vaccination remains suboptimal. Despite the timing of the peak of influenza disease,

administration of vaccine decreases substantially after November. According to results from the NHIS regarding the two most recent influenza seasons for which these data are available, approximately 84% of all influenza vaccination were administered during September--November. Among persons aged ≥65 years, the percentage of September--November vaccinations was 92% (*346*). Because many persons recommended for vaccination remain unvaccinated at the end of November, CDC encourages public health partners and health-care providers to conduct vaccination clinics and other activities that promote influenza vaccination annually during National Influenza Vaccination Week and throughout the remainder of the influenza season.

Self-report of influenza vaccination among adults, compared with determining vaccination status from the medical record, is a sensitive and specific source of information (*347*). Patient self-reports should be accepted as evidence of influenza vaccination in clinical practice (*347*). However, information on the validity of parents' reports of pediatric influenza vaccination is not yet available.

Recommendations for Using TIV and LAIV During the 2008--09 Influenza Season

Both TIV and LAIV prepared for the 2008--09 season will include A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens. These viruses will be used because they are representative of influenza viruses that are forecasted to be circulating in the United States during the 2008--09 influenza season and have favorable growth properties in eggs.

TIV and LAIV can be used to reduce the risk for influenza virus infection and its complications. Vaccination providers should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected.

Healthy, nonpregnant persons aged 2--49 years can choose to receive either vaccine. Some TIV formulations are FDA-licensed for use in persons as young as age 6 months (see Recommended Vaccines for Different Age Groups). TIV is licensed for use in persons with high-risk conditions. LAIV is FDA-licensed for use only for persons aged 2--49 years. In addition, FDA has indicated that the safety of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications. All children aged 6 months--8 years who have not been vaccinated previously at any time with at least 1 dose of either LAIV or TIV should receive 2 doses of age-appropriate vaccine in the same season, with a single dose during subsequent seasons.

Target Groups for Vaccination

Influenza vaccine should be provided to all persons who want to reduce the risk of becoming ill with influenza or of transmitting it to others. However, emphasis on providing routine vaccination annually to certain groups at higher risk for influenza infection or complications is advised, including all children aged 6 months--18 years, all persons aged ≥50 years, and other adults at risk for medical complications from influenza or more likely to require medical care should receive influenza vaccine annually. In addition, all persons who live with or care for persons at high risk for influenza-related complications, including contacts of children aged <6 months, should receive influenza vaccine annually (Boxes 1 and 2). Approximately 83% of the United States population is included in one or more of these target groups; however, <40% of the U.S. population received an influenza vaccination during 2007--2008.

Children Aged 6 Months--18 Years

Beginning with the 2008--09 influenza season, annual vaccination for all children aged 6 months--18 years is recommended. Annual vaccination of all children aged 6 months--4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue. Children and adolescents at high risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children. Annual vaccination of all children aged 5--18 years should begin in September 2008 or as soon as vaccine is available for the 2008--09 influenza season, if feasible. Annual vaccination of all children aged 5--18 years should begin no later than during the 2009--10 influenza season.

Healthy children aged 2--18 years can receive either LAIV or TIV. Children aged 6--23 months, those aged 2--4 years who have evidence of possible reactive airways disease (see Considerations When Using LAIV) or who have medical conditions that put them at higher risk for influenza complications should receive TIV. All children aged 6 months--8 years who have not received vaccination against influenza previously should receive 2 doses of vaccine the first year they are vaccinated.

Persons at Risk for Medical Complications

Vaccination to prevent influenza is particularly important for the following persons who are at increased risk for severe complications from influenza, or at higher risk for influenza-associated clinic, emergency department, or hospital visits. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to these persons:

- all children aged 6 months--4 years (59 months);
- all persons aged ≥50 years;

- children and adolescents (aged 6 months--18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- women who will be pregnant during the influenza season;
- adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus);
- adults and children who have immunosuppression (including immunosuppression caused by medications or by HIV);
- adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; and
- residents of nursing homes and other chronic-care facilities.

Persons Who Live With or Care for Persons at High Risk for Influenza-Related Complications

To prevent transmission to persons identified above, vaccination with TIV or LAIV (unless contraindicated) also is recommended for the following persons. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to these persons:

- HCP;
- healthy household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years; and
- healthy household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

Additional Information About Vaccination of Specific Populations

Children Aged 6 Months--18 Years

Beginning with the 2008--09 influenza season, all children aged 6 months--18 years should be vaccinated against influenza annually. The expansion of vaccination to include all children aged 5--18 years should begin in 2008 if feasible, but no later than the 2009--10 influenza season. In 2004, ACIP recommended routine vaccination for all children aged 6--23 months, and in 2006, ACIP expanded the recommendation to include all children aged 24--59 months. The committee's recommendation to expand routine influenza vaccination to include all school-age children and adolescents aged 5--18 years is based on 1) accumulated evidence that influenza vaccine is effective and safe for school-aged children (see "Influenza Vaccine Efficacy, Effectiveness, and Safety"), 2) increased evidence that influenza has substantial adverse impacts among school-aged children and their contacts (e.g., school absenteeism, increased antibiotic use, medical care visits, and parental work

loss) (see "Health-Care Use, Hospitalizations, and Deaths Attributed to Influenza"), and, 3) an expectation that a simplified age-based influenza vaccine recommendation for all school-age children and adolescents will improve vaccine coverage levels among the approximately 50% of school-aged children who already had a risk- or contact-based indication for annual influenza vaccination.

Children typically have the highest attack rates during community outbreaks of influenza and serve as a major source of transmission within communities (*1,2*). If sufficient vaccination coverage among children can be achieved, evidence for additional benefits, such as the indirect effect of reducing influenza among persons who have close contact with children and reducing overall transmission within communities, might occur. Achieving and sustaining community-level reductions in influenza will require mobilization of community resources and development of sustainable annual vaccination campaigns to assist health-care providers and vaccination programs in providing influenza vaccination services to children of all ages. In many areas, innovative community-based efforts, which might include mass vaccination programs in school or other community settings, will be needed to supplement vaccination services provided in health-care providers' offices or public health clinics. In nonrandomized community-based controlled trials, reductions in ILI-related symptoms and medical visits among household contacts have been demonstrated in communities where vaccination programs among school-aged children were established, compared with communities without such vaccination programs (*299--301*). Rates of school absences associated with ILI also were significantly reduced in some studies. In addition, reducing influenza transmission among children through vaccination has reduced rates for self-reported ILI among household contacts and among unvaccinated children (*297,298*).

Reducing influenza-related illness among children who are at high risk for influenza complications should continue to be a primary focus of influenza-prevention efforts. Children who should be vaccinated because they are at high risk for influenza complications include all children aged 6--59 months, children with certain medical conditions, children who are contacts of children aged <5 years (60 months) or persons aged ≥50 years, and children who are contacts of persons at high risk for influenza complications because of medical conditions. Influenza vaccines are not licensed by FDA for use among children aged <6 months. Because these infants are at higher risk for influenza complications compared with other child age groups, prevention efforts that focus on vaccinating household contacts and out-of-home caregivers to reduce the risk for influenza in these infants is a high priority.

All children aged 6 months--8 years who have not received vaccination against influenza previously should receive 2 doses of vaccine the first influenza season

that they are vaccinated. The second dose should be administered 4 or more weeks after the initial dose. For example, children aged 6 months--8 years who were vaccinated for the first time during the 2007--08 influenza season but only received 1 dose during that season should receive 2 doses of the 2008--09 influenza vaccine. All other children aged 6 months--8 years who have previously received 1 or more doses of influenza vaccine at any time should receive 1 dose of the 2008--09 influenza vaccine. Children aged 6 months--8 years who only received a single vaccination during a season before 2007--08 should receive 1 dose of the 2008--09 influenza vaccine. If possible, both doses should be administered before onset of influenza season. However, vaccination, including the second dose, is recommended even after influenza virus begins to circulate in a community.

HCP and Other Persons Who Can Transmit Influenza to Those at High Risk

Healthy persons who are infected with influenza virus, including those with subclinical infection, can transmit influenza virus to persons at higher risk for complications from influenza. In addition to HCP, groups that can transmit influenza to high-risk persons and that should be vaccinated include

- employees of assisted living and other residences for persons in groups at high risk;
- persons who provide home care to persons in groups at high risk; and
- household contacts (including children) of persons in groups at high risk.

In addition, because children aged <5 years are at increased risk for influenza-related hospitalization (*7,37,58,63,348*) compared with older children, vaccination is recommended for their household contacts and out-of-home caregivers. Because influenza vaccines have not been licensed by FDA for use among children aged <6 months, emphasis should be placed on vaccinating contacts of children aged <6 months. When vaccine supply is limited, priority for vaccination should be given to contacts of children aged <6 months.

Healthy HCP and persons aged 2--49 years who are contacts of persons in these groups and who are not contacts of severely immunosuppressed persons (see Close Contacts of Immunocompromised Persons) should receive either LAIV or TIV when indicated or requested. All other persons, including pregnant women, should receive TIV.

All HCP, as well as those in training for health-care professions, should be vaccinated annually against influenza. Persons working in health-care settings who should be vaccinated include physicians, nurses, and other workers in both hospital and outpatient-care settings, medical emergency-response workers (e.g., paramedics and emergency medical technicians), employees of nursing

home and chronic-care facilities who have contact with patients or residents, and students in these professions who will have contact with patients (*339,340,349*).

Facilities that employ HCP should provide vaccine to workers by using approaches that have been demonstrated to be effective in increasing vaccination coverage. Health-care administrators should consider the level of vaccination coverage among HCP to be one measure of a patient safety quality program and consider obtaining signed declinations from personnel who decline influenza vaccination for reasons other than medical contraindications (*340*). Influenza vaccination rates among HCP within facilities should be regularly measured and reported, and ward-, unit-, and specialty-specific coverage rates should be provided to staff and administration (*340*). Studies have demonstrated that organized campaigns can attain higher rates of vaccination among HCP with moderate effort and by using strategies that increase vaccine acceptance (*338,340,350*).

Efforts to increase vaccination coverage among HCP are supported by various national accrediting and professional organizations and in certain states by statute. The Joint Commission on Accreditation of Health-Care Organizations has approved an infection-control standard that requires accredited organizations to offer influenza vaccinations to staff, including volunteers and licensed independent practitioners with close patient contact. The standard became an accreditation requirement beginning January 1, 2007 (*351*). In addition, the Infectious Diseases Society of America recommended mandatory vaccination for HCP, with a provision for declination of vaccination based on religious or medical reasons (*352*). Fifteen states have regulations regarding vaccination of HCP in long-term--care facilities (*353*), six states require that health-care facilities offer influenza vaccination to HCP, and four states require that HCP either receive influenza vaccination or indicate a religious, medical, or philosophical reason for not being vaccinated (*354,355*).

Close Contacts of Immunocompromised Persons

Immunocompromised persons are at risk for influenza complications but might have insufficient responses to vaccination. Close contacts of immunocompromised persons, including HCP, should be vaccinated to reduce the risk for influenza transmission. TIV is preferred for vaccinating household members, HCP, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment (typically defined as a specialized patient-care area with a positive airflow relative to the corridor, high-efficiency particulate air filtration, and frequent air changes) (*340,356*).

LAIV transmission from a recently vaccinated person causing clinically important illness in an immunocompromised contact has not been reported. The rationale for avoiding use of LAIV among HCP or other close contacts of severely immunocompromised patients is the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunosuppressed person. As a precautionary measure, HCP who receive LAIV should avoid providing care for severely immunosuppressed patients for 7 days after vaccination. Hospital visitors who have received LAIV should avoid contact with severely immunosuppressed persons in protected environments for 7 days after vaccination but should not be restricted from visiting less severely immunosuppressed patients.

No preference is indicated for TIV use by persons who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, persons with asthma who take corticosteroids, persons who have recently received chemotherapy or radiation but who are not being cared for in a protective environment as defined above, or persons infected with HIV) or for TIV use by HCP or other healthy nonpregnant persons aged 2--49 years in close contact with persons in all other groups at high risk.

Pregnant Women

Pregnant women are at risk for influenza complications, and all women who are pregnant or will be pregnant during influenza season should be vaccinated. The American College of Obstetricians and Gynecologists and the American Academy of Family Physicians also have recommended routine vaccination of all pregnant women (*357*). No preference is indicated for use of TIV that does not contain thimerosal as a preservative (see Vaccine Preservative [Thimerosal] in Multidose Vials of TIV) for any group recommended for vaccination, including pregnant women. LAIV is not licensed for use in pregnant women. However, pregnant women do not need to avoid contact with persons recently vaccinated with LAIV.

Breastfeeding Mothers

Vaccination is recommended for all persons, including breastfeeding women, who are contacts of infants or children aged ≤59 months (i.e., <5 years), because infants and young children are at high risk for influenza complications and are more likely to require medical care or hospitalization if infected. Breastfeeding does not affect the immune response adversely and is not a contraindication for vaccination (*197*). Women who are breastfeeding can receive either TIV or LAIV unless contraindicated because of other medical conditions.

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the temperate regions of the Southern Hemisphere, influenza activity occurs typically during April--September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large tourist groups (e.g., on cruise ships) that include persons from areas of the world in which influenza viruses are circulating (*358,359*). In the tropics, influenza occurs throughout the year. In a study among Swiss travelers to tropical and subtropical countries, influenza was the most frequently acquired vaccine-preventable disease (*360*).

Any traveler who wants to reduce the risk for influenza infection should consider influenza vaccination, preferably at least 2 weeks before departure. In particular, persons at high risk for complications of influenza and who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to

- travel to the tropics,
- travel with organized tourist groups at any time of year, or
- travel to the Southern Hemisphere during April--September.

No information is available about the benefits of revaccinating persons before summer travel who already were vaccinated during the preceding fall. Persons at high risk who receive the previous season's vaccine before travel should be revaccinated with the current vaccine the following fall or winter. Persons at higher risk for influenza complications should consult with their health-care practitioner to discuss the risk for influenza or other travel-related diseases before embarking on travel during the summer.

General Population

Vaccination is recommended for any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected. Healthy, nonpregnant persons aged 2--49 years might choose to receive either TIV or LAIV. All other persons aged ≥6 months should receive TIV. Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories or correctional facilities) should be encouraged to receive vaccine to minimize morbidity and the disruption of routine activities during epidemics (*361,362*).

Recommended Vaccines for Different Age Groups

When vaccinating children aged 6--35 months with TIV, health-care providers should use TIV that has been licensed by the FDA for this age group (i.e., TIV manufactured by Sanofi Pasteur ([FluZone]). TIV from Novartis (Fluvirin) is FDA-approved in the United States for use among persons aged ≥4 years. TIV from GlaxoSmithKline (Fluarix and FluLaval) or CSL Biotherapies (Afluria) is labeled for use in persons aged ≥18 years because data to demonstrate efficacy among younger persons have not been provided to FDA. LAIV from MedImmune (FluMist) is licensed for use by healthy nonpregnant persons aged 2--49 years (Table 1). A vaccine dose does not need to be repeated if inadvertently administered to a person who does not have an age indication for the vaccine formulation given. Expanded age and risk group indications for licensed vaccines are likely over the next several years, and vaccination providers should be alert to these changes. In addition, several new vaccine formulations are being evaluated in immunogenicity and efficacy trials; when licensed, these new products will increase the influenza vaccine supply and provide additional vaccine choices for practitioners and their patients.

Influenza Vaccines and Use of Influenza Antiviral Medications

Administration of TIV and influenza antivirals during the same medical visit is acceptable. The effect on safety and effectiveness of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antivirals reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV. Persons receiving antivirals within the period 2 days before to 14 days after vaccination with LAIV should be revaccinated at a later date (*197*,*252*).

Persons Who Should Not Be Vaccinated with TIV

TIV should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. Information about vaccine components is located in package inserts from each manufacturer. Persons with moderate to severe acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate use of influenza vaccine. GBS within 6 weeks following a previous dose of TIV is considered to be a precaution for use of TIV.

Considerations When Using LAIV

LAIV is an option for vaccination of healthy, nonpregnant persons aged 2--49 years, including HCP and other close contacts of high-risk persons (excepting

severely immunocompromised persons who require care in a protected environment). No preference is indicated for LAIV or TIV when considering vaccination of healthy, nonpregnant persons aged 2--49 years. Use of the term "healthy" in this recommendation refers to persons who do not have any of the underlying medical conditions that confer high risk for severe complications (see Persons Who Should Not Be Vaccinated with LAIV). However, during periods when inactivated vaccine is in short supply, use of LAIV is encouraged when feasible for eligible persons (including HCP) because use of LAIV by these persons might increase availability of TIV for persons in groups targeted for vaccination, but who cannot receive LAIV. Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response in children, its ease of administration, and the possibly increased acceptability of an intranasal rather than intramuscular route of administration.

If the vaccine recipient sneezes after administration, the dose should not be repeated. However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness, or TIV should be administered instead. No data exist about concomitant use of nasal corticosteroids or other intranasal medications (*252*).

Although FDA licensure of LAIV excludes children aged 2--4 years with a history of asthma or recurrent wheezing, the precise risk, if any, of wheezing caused by LAIV among these children is unknown because experience with LAIV among these young children is limited. Young children might not have a history of recurrent wheezing if their exposure to respiratory viruses has been limited because of their age. Certain children might have a history of wheezing with respiratory illnesses but have not had asthma diagnosed. The following screening recommendations should be used to assist persons who administer influenza vaccines in providing the appropriate vaccine for children aged 2--4 years.

Clinicians and vaccination programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2--4 years, and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health-care providers should consult the medical record, when available, to identify children aged 2--4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2--4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months should not receive

LAIV. TIV is available for use in children with asthma or possible reactive airways diseases (*363*).

LAIV can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness.

Persons Who Should Not Be Vaccinated with LAIV

The effectiveness or safety of LAIV is not known for the following groups, and these persons should not be vaccinated with LAIV:

- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs.
- persons aged <2 years or those aged ≥50 years;
- persons with any of the underlying medical conditions that serve as an indication for routine influenza vaccination, including asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies; or known or suspected immunodeficiency diseases or immunosuppressed states;
- children aged 2--4 years whose parents or caregivers report that a health-care provider has told them during the preceding 12 months that their child had wheezing or asthma, or whose medical record indicates a wheezing episode has occurred during the preceding 12 months;
- children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza virus infection);
- persons with a history of GBS after influenza vaccination; or
- pregnant women.

Personnel Who Can Administer LAIV

Low-level introduction of vaccine viruses into the environment probably is unavoidable when administering LAIV. The risk for acquiring vaccine viruses from the environment is unknown but is probably low. Severely immunosuppressed persons should not administer LAIV. However, other persons at higher risk for influenza complications can administer LAIV. These include persons with underlying medical conditions placing them at higher risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged ≥50 years.

Concurrent Administration of Influenza Vaccine with Other Vaccines

Use of LAIV concurrently with measles, mumps, rubella (MMR) alone and MMR and varicella vaccine among children aged 12--15 months has been studied, and no interference with the immunogenicity to antigens in any of the vaccines was observed (*252,364*). Among adults aged ≥50 years, the safety and immunogenicity of zoster vaccine and TIV was similar whether administered simultaneously or spaced 4 weeks apart (*365*). In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent (*197*). Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. Inactivated or live vaccines can be administered simultaneously with LAIV. However, after administration of a live vaccine, at least 4 weeks should pass before another live vaccine is administered.

Recommendations for Vaccination Administration and Vaccination Programs

Although influenza vaccination levels increased substantially during the 1990s, little progress has been made toward achieving national health objectives, and further improvements in vaccine coverage levels are needed. Strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs (*325,366,367*), should be implemented whenever feasible. Vaccination coverage can be increased by administering vaccine before and during the influenza season to persons during hospitalizations or routine health-care visits. Vaccinations can be provided in alternative settings (e.g., pharmacies, grocery stores, workplaces, or other locations in the community), thereby making special visits to physicians' offices or clinics unnecessary. Coordinated campaigns such as the National Influenza Vaccination Week (December 8--14, 2008) provide opportunities to refocus public attention on the benefits, safety, and availability of influenza vaccination throughout the influenza season. When educating patients about potential adverse events, clinicians should emphasize that 1) TIV contains noninfectious killed viruses and cannot cause influenza, 2) LAIV contains weakened influenza viruses that cannot replicate outside the upper respiratory tract and are unlikely to infect others, and 3) concomitant symptoms or respiratory disease unrelated to vaccination with either TIV or LAIV can occur after vaccination.

Information About the Vaccines for Children Program

The Vaccines for Children (VFC) program supplies vaccine to all states, territories, and the District of Columbia for use by participating providers. These vaccines are to be provided to eligible children without vaccine cost to the patient or the provider, although the provider might charge a vaccine administration fee. All routine childhood vaccines recommended by ACIP are available through this program, including influenza vaccines. The program saves parents and providers out-of-pocket expenses for vaccine purchases and

provides cost savings to states through CDC's vaccine contracts. The program results in lower vaccine prices and ensures that all states pay the same contract prices. Detailed information about the VFC program is available at http://www.cdc.gov/vaccines/programs/vfc/default.htm.

Influenza Vaccine Supply Considerations

The annual supply of influenza vaccine and the timing of its distribution cannot be guaranteed in any year. During the 2007--08 influenza season, 113 million doses of influenza vaccine were distributed in the United States. Total production of influenza vaccine for the United States is anticipated to be >130 million doses for the 2008--09 season, depending on demand and production yields. However, influenza vaccine distribution delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains and various other manufacturing and regulatory issues. To ensure optimal use of available doses of influenza vaccine, health-care providers, those planning organized campaigns, and state and local public health agencies should develop plans for expanding outreach and infrastructure to vaccinate more persons in targeted groups and others who wish to reduce their risk for influenza and develop contingency plans for the timing and prioritization of administering influenza vaccine if the supply of vaccine is delayed or reduced.

If supplies of TIV are not adequate, vaccination should be carried out in accordance with local circumstances of supply and demand based on the judgment of state and local health officials and health-care providers. Guidance for tiered use of TIV during prolonged distribution delays or supply shortfalls is available at http://www.cdc.gov/flu/professionals/vaccination/vax_priority.htm and will be modified as needed in the event of shortage. CDC and other public health agencies will assess the vaccine supply on a continuing basis throughout the manufacturing period and will inform both providers and the general public if any indication exists of a substantial delay or an inadequate supply.

Because LAIV is only recommended for use in healthy nonpregnant persons aged 2--49 years, no recommendations for prioritization of LAIV use are made. Either LAIV or TIV when considering vaccination of healthy, nonpregnant persons aged 2--49 years. However, during shortages of TIV, LAIV should be used preferentially when feasible for all healthy nonpregnant persons aged 2--49 years (including HCP) who desire or are recommended for vaccination to increase the availability of inactivated vaccine for persons at high risk.

Timing of Vaccination

Vaccination efforts should be structured to ensure the vaccination of as many persons as possible over the course of several months, with emphasis on

vaccinating before influenza activity in the community begins. Even if vaccine distribution begins before October, distribution probably will not be completed until December or January. The following recommendations reflect this phased distribution of vaccine.

In any given year, the optimal time to vaccinate patients cannot be precisely determined because influenza seasons vary in their timing and duration, and more than one outbreak might occur in a single community in a single year. In the United States, localized outbreaks that indicate the start of seasonal influenza activity can occur as early as October. However, in >80% of influenza seasons since 1976, peak influenza activity (which is often close to the midpoint of influenza activity for the season) has not occurred until January or later, and in >60% of seasons, the peak was in February or later (Figure 1). In general, health-care providers should begin offering vaccination soon after vaccine becomes available and if possible by October. To avoid missed opportunities for vaccination, providers should offer vaccination during routine health-care visits or during hospitalizations whenever vaccine is available.

Vaccination efforts should continue throughout the season, because the duration of the influenza season varies, and influenza might not appear in certain communities until February or March. Providers should offer influenza vaccine routinely, and organized vaccination campaigns should continue throughout the influenza season, including after influenza activity has begun in the community. Vaccine administered in December or later, even if influenza activity has already begun, is likely to be beneficial in the majority of influenza seasons. The majority of adults have antibody protection against influenza virus infection within 2 weeks after vaccination (*368,369*).

All children aged 6 months--8 years who have not received vaccination against influenza previously should receive their first dose as soon after vaccine becomes available as is feasible. This practice increases the opportunity for both doses to be administered before or shortly after the onset of influenza activity.

Persons and institutions planning substantial organized vaccination campaigns (e.g., health departments, occupational health clinics, and community vaccinators) should consider scheduling these events after at least mid-October because the availability of vaccine in any location cannot be ensured consistently in early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable. These vaccination clinics should be scheduled through December, and later if feasible, with attention to settings that serve children aged 6--59 months, pregnant women, other persons aged <50 years at increased risk for influenza-related complications, persons aged ≥50 years, HCP, and persons who are household

contacts of children aged ≤59 months or other persons at high risk. Planners are encouraged to develop the capacity and flexibility to schedule at least one vaccination clinic in December. Guidelines for planning large-scale vaccination clinics are available at http://www.cdc.gov/flu/professionals/vaccination/vax_clinic.htm.

During a vaccine shortage or delay, substantial proportions of TIV doses may not be released and distributed until November and December or later. When the vaccine is substantially delayed or disease activity has not subsided, providers should consider offering vaccination clinics into January and beyond as long as vaccine supplies are available. Campaigns using LAIV also can extend into January and beyond.

Strategies for Implementing Vaccination Recommendations in Health-Care Settings

Successful vaccination programs combine publicity and education for HCP and other potential vaccine recipients, a plan for identifying persons recommended for vaccination, use of reminder/recall systems, assessment of practice-level vaccination rates with feedback to staff, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs (*367,370*). The use of standing orders programs by long-term--care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies ensures that vaccination is offered. Standing orders programs for influenza vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by HCP trained to screen patients for contraindications to vaccination, administer vaccine, and monitor for adverse events. CMS has removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term--care facilities, and home health agencies (*371*). To the extent allowed by local and state law, these facilities and agencies can implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Payment for influenza vaccine under Medicare Part B is available (*372,373*). Other settings (e.g., outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs (*374*). In addition, physician reminders (e.g., flagging charts) and patient reminders are recognized strategies for increasing rates of influenza vaccination. Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following sections.

Outpatient Facilities Providing Ongoing Care

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) should identify and label the medical records of patients who should receive vaccination. Vaccine should be offered during visits throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record. Patients for whom vaccination is recommended and who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

Outpatient Facilities Providing Episodic or Acute Care

Acute health-care facilities (e.g., emergency departments and walk-in clinics) should offer vaccinations throughout the influenza season to persons for whom vaccination is recommended or provide written information regarding why, where, and how to obtain the vaccine. This written information should be available in languages appropriate for the populations served by the facility.

Nursing Homes and Other Residential Long-Term--Care Facilities

Vaccination should be provided routinely to all residents of chronic-care facilities. If possible, all residents should be vaccinated at one time before influenza season. In the majority of seasons, TIV will become available to long-term--care facilities in October or November, and vaccination should commence as soon as vaccine is available. As soon as possible after admission to the facility, the benefits and risks of vaccination should be discussed and education materials provided. Signed consent is not required (*375*). Residents admitted after completion of the vaccination program at the facility should be vaccinated at the time of admission through March.

Since October 2005, the Centers for Medicare and Medicaid Services (CMS) has required nursing homes participating in the Medicare and Medicaid programs to offer all residents influenza and pneumococcal vaccines and to document the results. According to the requirements, each resident is to be vaccinated unless contraindicated medically, the resident or a legal representative refuses vaccination, or the vaccine is not available because of shortage. This information is to be reported as part of the CMS Minimum Data Set, which tracks nursing home health parameters (*372,376*).

Acute-Care Hospitals

Hospitals should serve as a key setting for identifying persons at increased risk for influenza complications. Unvaccinated persons of all ages (including children) with high-risk conditions and persons aged 6 months--18 years or ≥50 years who are hospitalized at any time during the period when vaccine is

available should be offered and strongly encouraged to receive influenza vaccine before they are discharged. Standing orders to offer influenza vaccination to all hospitalized persons should be considered.

Visiting Nurses and Others Providing Home Care to Persons at High Risk

Nursing-care plans should identify patients for whom vaccination is recommended, and vaccine should be administered in the home, if necessary as soon as influenza vaccine is available and throughout the influenza season. Caregivers and other persons in the household (including children) should be referred for vaccination.

Other Facilities Providing Services to Persons Aged ≥50 Years

Facilities providing services to persons aged ≥50 years (e.g., assisted living housing, retirement communities, and recreation centers) should offer unvaccinated residents, attendees, and staff annual on-site vaccination before the start of the influenza season. Continuing to offer vaccination throughout the fall and winter months is appropriate. Efforts to vaccinate newly admitted patients or new employees also should be continued, both to prevent illness and to avoid having these persons serve as a source of new influenza infections. Staff education should emphasize the need for influenza vaccine.

Health-Care Personnel

Health-care facilities should offer influenza vaccinations to all HCP, including night, weekend, and temporary staff. Particular emphasis should be placed on providing vaccinations to workers who provide direct care for persons at high risk for influenza complications. Efforts should be made to educate HCP regarding the benefits of vaccination and the potential health consequences of influenza illness for their patients, themselves, and their family members. All HCP should be provided convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs (*340*,*350*,*351*).

Future Directions for Research and Recommendations Related to Influenza Vaccine

Although available influenza vaccines are effective and safe, additional research is needed to improve prevention efforts. Most mortality from influenza occurs among person aged ≥65 years (*6*), and more immunogenic influenza vaccines are needed for this age group and other risk groups at high risk for mortality. Additional research is also needed to understand potential biases in estimating the benefits of vaccination among older adults in reducing hospitalizations and deaths (*101,193,377*). Additional studies of the relative cost-effectiveness and cost utility of influenza vaccination among children and adults, especially those aged <65 years, are needed and should be designed to

account for year-to-year variations in influenza attack rates, illness severity, hospitalization costs and rates, and vaccine effectiveness when evaluating the long-term costs and benefits of annual vaccination (*378*). Additional data on indirect effects of vaccination are also needed to quantify the benefits of influenza vaccination of HCP in protecting their patients (*294*) and the benefits of vaccinating children to reduce influenza complications among those at risk. Because of expansions in ACIP recommendations for vaccination will lead to more persons being vaccinated, much larger research networks are needed that can identify and assess the causality of very rare events that occur after vaccination, including GBS. These research networks could also provide a platform for effectiveness and safety studies in the event of a pandemic. Research on potential biologic or genetic risk factors for GBS also is needed. In addition, a better understanding of how to motivate persons at risk to seek annual influenza vaccination is needed.

ACIP continues to review new vaccination strategies to protect against influenza, including the possibility of expanding routine influenza vaccination recommendations toward universal vaccination or other approaches that will help reduce or prevent the transmission of influenza and reduce the burden of severe disease (*379*--*384*). The expansion of annual vaccination recommendations to include all children aged 6 months--18 years will require a substantial increase in resources for epidemiologic research to develop long term studies capable of assessing the possible effects on community-level transmission. Additional planning to improve surveillance systems capable of monitoring effectiveness, safety and vaccine coverage, and further development of implementation strategies will also be necessary. In addition, as noted by the National Vaccine Advisory Committee, strengthening the U.S. influenza vaccination system will require improving vaccine financing and demand and implementing systems to help better understand the burden of influenza in the United States (*385*). Vaccination programs capable of delivering annual influenza vaccination to a broad range of the population could potentially serve as a resilient and sustainable platform for delivering vaccines and monitoring outcomes for other urgently required public health interventions (e.g., vaccines for pandemic influenza or medications to prevent or treat illnesses caused by acts of terrorism).

Seasonal Influenza Vaccine and Avian or Swine Influenza

Human infection with novel or nonhuman influenza A virus strains, including influenza A viruses of animal origin, is a nationally notifiable disease (*386*). Human infections with nonhuman or novel human influenza A virus should be identified quickly and investigated to determine possible sources of exposure, identify additional cases, and evaluate the possibility of human-to-human transmission because transmission patterns could change over time with variations in these influenza A viruses.

Sporadic severe and fatal human cases of infection with highly pathogenic avian influenza A(H5N1) viruses have been identified in Asia, Africa, Europe and the Middle East, primarily among persons who have had direct or close unprotected contact with sick or dead birds associated with the ongoing H5N1 panzootic among birds (*387--392*). Limited, nonsustained human-to-human transmission of H5N1 viruses has likely occurred in some case clusters (*393,394*). To date, no evidence exists of genetic reassortment between human influenza A and H5N1 viruses. However, influenza viruses derived from strains circulating among poultry (e.g., the H5N1 viruses that have caused outbreaks of avian influenza and occasionally have infected humans) have the potential to recombine with human influenza A viruses (*395,396*). To date, highly pathogenic H5N1 viruses have not been identified in wild or domestic birds or in humans in the United States.

Human illness from infection with different avian influenza A subtype viruses also have been documented, including infections with low pathogenic and highly pathogenic viruses. A range of clinical illness has been reported for human infection with low pathogenic avian influenza viruses, including conjunctivitis with influenza A(H7N7) virus in the U.K., lower respiratory tract disease and conjunctivitis with influenza A(H7N2) virus in the U.K., and uncomplicated influenza-like illness with influenza A(H9N2) virus in Hong Kong and China (*397--402*). Two human cases of infection with low pathogenic influenza A(H7N2) were reported in the United States (*400*). Although human infections with highly pathogenic A(H7N7) virus infections typically have influenza-like illness or conjunctivitis, severe infections, including one fatal case in the Netherlands, have been reported (*403,404*). Conjunctivitis has also been reported because of human infection with highly pathogenic influenza A(H7N3) virus in Canada and low pathogenic A(H7N3) in the U.K (*397,404*). In contrast, sporadic infections with highly pathogenic avian influenza A(H5N1) viruses have caused severe illness in many countries, with an overall case-fatality ratio of >60% (*394,405*).

Swine influenza A(H1N1), A(H1N2), and A(H3N2) viruses are endemic among pig populations in the United States (*406*), including reassortant viruses. Two clusters of influenza A(H2N3) virus infections among pigs have been recently reported (*407*). Outbreaks among pigs normally occur in colder weather months (late fall and winter) and sometimes with the introduction of new pigs into susceptible herds. An estimated 30% of the pig population in the United States has serologic evidence of having had swine influenza A(H1N1) virus infection. Sporadic human infections with swine influenza A viruses occur in the United States, but the frequency of these human infections is unknown. Persons infected with swine influenza A viruses typically report direct contact with ill pigs or places where pigs have been present (e.g., agricultural fairs or farms), and have symptoms that are clinically indistinguishable from infection with other

respiratory viruses (*408*). Clinicians should consider swine influenza A virus infection in the differential diagnosis of patients with ILI who have had recent contact with pigs. The sporadic cases identified in recent years have not resulted in sustained human-to-human transmission of swine influenza A viruses or community outbreaks. Although immunity to swine influenza A viruses appears to be low in the overall human population (<2%), 10%--20% of persons occupationally exposed to pigs (e.g., pig farmers or pig veterinarians) have been documented in certain studies to have antibody evidence of prior swine influenza A(H1N1) virus infection (*409,410*).

Current seasonal influenza vaccines are not expected to provide protection against human infection with avian influenza A viruses, including H5N1 viruses, or to provide protection against currently circulating swine influenza A viruses. However, reducing seasonal influenza risk through influenza vaccination of persons who might be exposed to nonhuman influenza viruses (e.g., H5N1 viruses) might reduce the theoretical risk for recombination of influenza A viruses of animal origin and human influenza A viruses by preventing seasonal influenza A virus infection within a human host.

CDC has recommended that persons who are charged with responding to avian influenza outbreaks among poultry receive seasonal influenza vaccination (*411*). As part of preparedness activities, the Occupational Safety and Health Administration (OSHA) has issued an advisory notice regarding poultry worker safety that is intended for implementation in the event of a suspected or confirmed avian influenza outbreak at a poultry facility in the United States. OSHA guidelines recommend that poultry workers in an involved facility receive vaccination against seasonal influenza; OSHA also has recommended that HCP involved in the care of patients with documented or suspected avian influenza should be vaccinated with the most recent seasonal human influenza vaccine to reduce the risk for co-infection with human influenza A viruses (*412*).

Recommendations for Using Antiviral Agents for Seasonal Influenza

Annual vaccination is the primary strategy for preventing complications of influenza virus infections. Antiviral medications with activity against influenza viruses are useful adjuncts in the prevention of influenza, and effective when used early in the course of illness for treatment. Four influenza antiviral agents are licensed in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Influenza A virus resistance to amantadine and rimantadine can emerge rapidly during treatment. Because antiviral testing results indicated high levels of resistance (*413--416*), neither amantadine nor rimantadine should be used for the treatment or chemoprophylaxis of influenza A in the United States during the 2007--08 influenza season. Surveillance demonstrating that susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses will be needed before amantadine or rimantadine

can be used for the treatment or chemoprophylaxis of influenza A. Oseltamivir or zanamivir can be prescribed if antiviral chemoprophylaxis or treatment of influenza is indicated. Oseltamivir is licensed for treatment of influenza in persons aged ≥1 year, and zanamivir is licensed for treating influenza in persons aged ≥7 years. Oseltamivir and zanamivir can be used for chemoprophylaxis of influenza; oseltamivir is licensed for use as chemoprophylaxis in persons aged ≥1 year, and zanamivir is licensed for use in persons aged ≥5 years.

During the 2007--08 influenza season, influenza A (H1N1) viruses with a mutation that confers resistance to oseltamivir were identified in the United States and other countries. As of June 27, 2008, in the United States, 111 (7.6%) of 1,464 influenza A viruses tested, and none of 305 influenza B viruses tested have been found to be resistant to oseltamivir. All of the resistant viruses identified in the United States and elsewhere are influenza A (H1N1) viruses. Of 1020 influenza A (H1N1) viruses isolated from patients in the United States, 111 (10.9%) exhibited a specific genetic mutation that confers oseltamivir resistance (*417*). Influenza A (H1N1) virus strains that are resistant to oseltamivir remain sensitive to zanamivir. Neuraminidase inhibitor medications continue to be the recommended agents for treatment and chemoprophylaxis of influenza in the United States. However, clinicians should be alert to changes in antiviral recommendations that might occur as additional antiviral resistance data becomes available during the 2008--09 influenza season (http://www.cdc.gov/flu/professionals/antivirals/index.htm).

Role of Laboratory Diagnosis

Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. However, only 69% of practitioners in one recent survey indicated that they test patients for influenza during the influenza season (*418*). The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza (*26,39,40*) (see Clinical Signs and Symptoms of Influenza).

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, reverse transcriptase-polymerase chain reaction (RT-PCR), and immunofluorescence assays (*419*). As with any diagnostic test, results should be evaluated in the context of other clinical and epidemiologic information available to health-care providers. Sensitivity and specificity of any test for influenza can vary by the laboratory that performs the test, the type of test used, the type of specimen tested, the quality of the specimen, and the timing of specimen collection in relation to illness onset. Among respiratory specimens for viral isolation or rapid detection of influenza viruses, nasopharyngeal and

nasal specimens have higher yields than throat swab specimens (*420*). In addition, positive influenza tests have been reported up to 7 days after receipt of LAIV (*421*).

Commercial rapid diagnostic tests are available that can detect influenza viruses within 30 minutes (*422,423*). Certain tests are licensed for use in any outpatient setting, whereas others must be used in a moderately complex clinical laboratory. These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types; or 3) both influenza A and B and distinguish between the two. None of the rapid influenza diagnostic tests specifically identifies any influenza A virus subtypes.

The types of specimens acceptable for use (i.e., throat, nasopharyngeal, or nasal aspirates, swabs, or washes) also vary by test, but all perform best when collected as close to illness onset as possible. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test (*419,422--424*). Rapid tests for influenza have high specificity (>90%), but are only moderately sensitive (<70%). A recent study found sensitivity to be as low as 42% in clinical practice (*425*). Rapid tests appear to have higher sensitivity when used in young children, compared with adults, possibly because young children with influenza typically shed higher concentrations of influenza viruses than adults (*426*). Since RT-PCR has high sensitivity to detect influenza virus infection compared to viral culture, rapid tests have lower sensitivity than viral culture when compared to RT-PCR.

The limitations of rapid diagnostic tests must be understood in order to properly interpret results. Positive rapid influenza test results are generally reliable when community influenza activity is high and are useful in deciding whether to initiate antiviral treatment. Negative rapid test results are less helpful in making treatment decisions for individual patients when influenza activity in a community is high. Because of the lower sensitivity of the rapid tests, physicians should consider confirming negative tests with viral culture or other means because of the possibility of false-negative rapid test results, especially during periods of peak community influenza activity. The positive predictive value of rapid tests will be lower during periods of low influenza activity, and clinicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community when interpreting results (*424*). When local influenza activity is high, persons with severe respiratory symptoms or persons with acute respiratory illness who are at higher risk for influenza complications should still be considered for influenza antiviral treatment despite a negative rapid influenza test unless illness can be attributed to another cause. However, because certain bacterial infections can produce

symptoms similar to influenza, if bacterial infections are suspected, they should be considered and treated appropriately. In addition, secondary invasive bacterial infections can be a severe complication of influenza. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests. Additional updated information concerning diagnostic testing is available at http://www.cdc.gov/flu/professionals/labdiagnosis.htm.

Despite the availability of rapid diagnostic tests, clinical specimens collected in virus surveillance systems for viral culture are critical for surveillance purposes. Only culture isolates of influenza viruses can provide specific information regarding circulating strains and subtypes of influenza viruses and data on antiviral resistance. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor antiviral resistance and the emergence of novel human influenza A virus subtypes that might pose a pandemic threat. Influenza surveillance by state and local health departments and CDC can provide information regarding the circulation of influenza viruses in the community, which can help inform decisions about the likelihood that a compatible clinical syndrome is indeed influenza.

Antiviral Agents for Influenza

Zanamivir and oseltamivir are chemically related antiviral medications known as neuraminidase inhibitors that have activity against both influenza A and B viruses. The two medications differ in pharmacokinetics, adverse events, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary adverse events of these medications is presented in the following sections. Package inserts should be consulted for additional information. Detailed information about amantadine and rimantadine (adamantanes) is available in previous ACIP influenza recommendations (*427*).

Indications for Use of Antivirals

Treatment

Initiation of antiviral treatment within 2 days of illness onset is recommended, although the benefit of treatment is greater as the time after illness onset is reduced. Certain persons have a high priority for treatment (Box 3); however, treatment does not need to be limited to these persons. In clinical trials conducted in outpatient settings, the benefit of antiviral treatment for uncomplicated influenza was minimal unless treatment was initiated within 48 hours after illness onset. However, no data are available on the benefit for

severe influenza when antiviral treatment is initiated >2 days after illness onset. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

Evidence for the efficacy of these antiviral drugs is based primarily on studies of outpatients with uncomplicated influenza. When administered within 2 days of illness onset to otherwise healthy children or adults, zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day compared with placebo (*143,428--442*). Minimal or no benefit was reported when antiviral treatment is initiated >2 days after onset of uncomplicated influenza. Data on whether viral shedding is reduced are inconsistent. The duration of viral shedding was reduced in one study that employed experimental infection; however, other studies have not demonstrated reduction in the duration of viral shedding. A recent review that examined neuraminidase inhibitor effect on reducing ILI concluded that neuraminidase inhibitors were not effective in the control of seasonal influenza (*443*). However, lower or no effectiveness using a nonspecific (compared with laboratory-confirmed influenza) clinical endpoint such as ILI would be expected (*444*).

Data are limited about the effectiveness of zanamivir and oseltamivir in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases), or for preventing influenza among persons at high risk for serious complications of influenza. In a study that combined data from 10 clinical trials, the risk for pneumonia among those participants with laboratory-confirmed influenza receiving oseltamivir was approximately 50% lower than among those persons receiving a placebo and 34% lower among patients at risk for complications ($p<0.05$ for both comparisons) (*445*). Although a similar significant reduction also was determined for hospital admissions among the overall group, the 50% reduction in hospitalizations reported in the small subset of high-risk participants was not statistically significant. One randomized controlled trial documented a decreased incidence of otitis media among children treated with oseltamivir (*437*). Another randomized controlled study conducted among influenza-infected children with asthma demonstrated significantly greater improvement in lung function and fewer asthma exacerbations among oseltamivir-treated children compared with those who received placebo but did not determine a difference in symptom duration (*446*). Inadequate data exist regarding the efficacy of any of the influenza antiviral drugs for use among children aged <1 year, and none are FDA-licensed for use in this age group.

Two observational studies suggest that oseltamivir reduces severe clinical outcomes in patients hospitalized with influenza. A large prospective observational study assessed clinical outcomes among 327 hospitalized adults

with laboratory-confirmed influenza whose health-care provider chose to use oseltamivir treatment compared to untreated influenza patients. The average age of adults in this study was 77 years, and 71% began treatment >48 hours after illness onset. In the multivariate analysis, oseltamivir treatment was associated with a significantly decreased risk for death within 15 days of hospitalization (odds ratio = 0.21; CI = 0.06--0.80). Benefit was observed even among those starting treatment >48 hours after symptom onset. However, oseltamivir treatment did not significantly reduce the duration of hospitalization or 30 day mortality after hospitalization. An additional 185 hospitalized children with laboratory confirmed influenza were identified during this study, but none received antiviral treatment and no assessment of outcomes based on receipt of antiviral treatment could be made (*95*). A retrospective cohort study of 99 hospitalized persons with laboratory-confirmed influenza administered who received oseltamivir that was conducted in Hong Kong reported that persons who received oseltamivir treatment >48 hours from illness onset had a median length of stay of 6 days compared to 4 days for persons who received oseltamivir within 48 hours of symptom onset ($p<0.0001$) (*447*). However, additional data on the impact of antiviral treatment on severe outcomes are needed.

More clinical data are available concerning the efficacy of zanamivir and oseltamivir for treatment of influenza A virus infection than for treatment of influenza B virus infection. Data from human clinical studies have indicated that zanamivir and oseltamivir have activity against influenza B viruses (*437,448--451*). However, an observational study among Japanese children with culture-confirmed influenza and treated with oseltamivir demonstrated that children with influenza A virus infection resolved fever and stopped shedding virus more quickly than children with influenza B, suggesting that oseltamivir might be less effective for the treatment of influenza B (*452*).

The Infectious Diseases Society of America and the American Thoracic Society have recommended that persons with community-acquired pneumonia and laboratory-confirmed influenza should receive either oseltamivir or zanamivir if treatment can be initiated within 48 hours of symptom onset. Patients who present >48 hours after illness onset are potential candidates for treatment if they have influenza pneumonia or to reduce viral shedding while hospitalized (*453*). The American Academy of Pediatrics recommends antiviral treatment of any child with influenza who is also at high risk of influenza complications, regardless of vaccination status, and any otherwise healthy child with moderate-to-severe influenza infection who might benefit from the decrease in duration of clinical symptoms documented to occur with therapy (*454*).

Chemoprophylaxis

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in preventing and controlling influenza. Certain persons are at higher priority for chemoprophylaxis (Box 4); however, chemoprophylaxis does not need to be limited to these persons. In community studies of healthy adults, both oseltamivir and zanamivir had similar efficacy in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%) (*455,456*). Both antiviral agents also have prevented influenza illness among persons administered chemoprophylaxis after a household member had influenza diagnosed (efficacy: zanamivir, 72%--82%; oseltamivir, 68%--89%) (*455--459*). Studies have demonstrated moderate to excellent efficacy for prevention of influenza among patients in institutional settings (*460--465*). For example, a 6-week study of oseltamivir chemoprophylaxis among nursing home residents demonstrated a 92% reduction in influenza illness (*464*). A 4-week study among community-dwelling persons at higher risk for influenza complications (median age: 60 years) demonstrated that zanamivir had an 83% effectiveness in preventing symptomatic laboratory-confirmed influenza (*465*). The efficacy of antiviral agents in preventing influenza among severely immunocompromised persons is unknown. A small nonrandomized study conducted in a stem cell transplant unit suggested that oseltamivir can prevent progression to pneumonia among influenza-infected patients (*466*).

When determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis, factors related to cost, compliance, and potential adverse events should be considered. To be maximally effective as chemoprophylaxis, the drug must be taken each day for the duration of influenza activity in the community. Additional clinical guidelines on the use of antiviral medications to prevent influenza are available (*453*,*454*).

Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun

Development of antibodies in adults after vaccination takes approximately 2 weeks (*369,370*). Therefore, when influenza vaccine is administered after influenza activity in a community has begun, chemoprophylaxis should be considered for persons at higher risk for influenza complications during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccination for the first time might require as much as 6 weeks of chemoprophylaxis (i.e., chemoprophylaxis until 2 weeks after the second dose when immunity after vaccination would be expected). Persons at higher risk for complications of influenza still can benefit from vaccination after community influenza activity has begun because influenza viruses might still be circulating at the time vaccine-induced immunity is achieved.

Persons Who Provide Care to Those at High Risk

To reduce the spread of virus to persons at high risk, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact might include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a strain of influenza that might not be covered by the vaccine, chemoprophylaxis can be considered for all such persons, regardless of their vaccination status.

Persons Who Have Immune Deficiencies

Chemoprophylaxis can be considered for persons at high risk who are more likely to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, particularly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if chemoprophylaxis is administered.

Other Persons

Chemoprophylaxis throughout the influenza season or during increases in influenza activity within the community might be appropriate for persons at high risk for whom vaccination is contraindicated, or for whom vaccination is likely to be ineffective. Health-care providers and patients should make decisions regarding whether to begin chemoprophylaxis and how long to continue it on an individual basis.

Antiviral Drug-Resistant Strains of Influenza

Oseltamivir and Zanamivir (Neuraminidase Inhibitors)

Among 2,287 isolates obtained from multiple countries during 1999--2002 as part of a global viral surveillance system, eight (0.3%) had a more than ten fold decrease in susceptibility to oseltamivir, and two (25%) of these eight also were resistant to zanamivir (*467*). In Japan, where more oseltamivir is used than in any other country, resistance to oseltamivir was identified in three (0.4%) A (H3N2) viruses in 2003--04, no A (H3N2) viruses in 2004--05, and no A (H3N2) viruses in 2005--06 influenza seasons. In 2005--06, four (2.2%) A (H1N1) viruses were identified to have oseltamivir resistance with a specific genetic marker (*468*). Neuraminidase inhibitor resistance remained low in the United States through the 2006--07 influenza season (CDC, unpublished data, 2007).

In 2007--08, increased resistance to oseltamivir was reported among A (H1N1) viruses in many countries (*469,470*). Persons infected with oseltamivir resistant A (H1N1) viruses had not previously received oseltamivir treatment and were

not known to have been exposed to a person undergoing oseltamivir treatment (*469,470*). In the United States, approximately 10% of influenza A (H1N1) viruses, no A (H3N2) viruses, and no influenza B viruses were resistant to oseltamivir during the 2007--08 influenza season, and the overall percentage of influenza A and B viruses resistant to oseltamivir in the United States was <5%. No viruses resistant to zanamivir were identified (*417*). Oseltamivir or zanamivir continue to be the antiviral agents recommended for the prevention and treatment of influenza (*418*). Although recommendations for use of antiviral medications have not changed, enhanced surveillance for detection of oseltamivir-resistant viruses is ongoing and will enable continued monitoring of changing trends over time.

Development of viral resistance to zanamivir or oseltamivir during treatment has also been identified but does not appear to be frequent (*450,471--474*). One limited study reported that oseltamivir-resistant influenza A viruses were isolated from nine (18%) of 50 Japanese children during treatment with oseltamivir (*475*). Transmission of neuraminidase inhibitor-resistant influenza B viruses acquired from persons treated with oseltamivir is rare but has been documented (*476*). No isolates with reduced susceptibility to zanamivir have been reported from clinical trials, although the number of post-treatment isolates tested is limited (*451,477*). Only one clinical isolate with reduced susceptibility to zanamivir, obtained from an immunocompromised child on prolonged therapy, has been reported (*451*). Prolonged shedding of oseltamivir- or zanamivir-resistant virus by severely immunocompromised patients, even after cessation of oseltamivir treatment, has been reported (*478,479*).

Amantadine and Rimantadine (Adamantanes)

Adamantane resistance among circulating influenza A viruses increased rapidly worldwide over the past several years, and these medications are no longer recommended for influenza prevention or treatment, although in some limited circumstances use of adamantanes in combination with a neuraminidase inhibitor medication might be considered (see Prevention and Treatment of Influenza when Oseltamivir Resistance is Suspected). The proportion of influenza A viral isolates submitted from throughout the world to the World Health Organization Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at CDC that were adamantane-resistant increased from 0.4% during 1994--1995 to 12.3% during 2003--2004 (*480*). During the 2005--06 influenza season, CDC determined that 193 (92%) of 209 influenza A (H3N2) viruses isolated from patients in 26 states demonstrated a change at amino acid 31 in the M2 gene that confers resistance to adamantanes (*413,414*). Preliminary data from the 2007--08 influenza season indicates that resistance to adamantanes remains high among influenza A isolates, with approximately 99% of tested influenza A(H3N2) isolates and approximately

10% of influenza A(H1N1) isolates resistant to adamantanes (CDC, unpublished data, 2008). Amantadine or rimantidine should not be used alone for the treatment or prevention of influenza in the United States until evidence of susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses. Adamantanes are not effective in the prevention or treatment of influenza B virus infections.

Prevention and Treatment of Influenza when Oseltamivir Resistance is Suspected

Testing for antiviral resistance in influenza viruses is not available in clinical settings. Because the proportion of influenza viruses that are resistant to oseltamivir remains <5% in the United States, oseltamivir or zanamivir remain the medications recommended for prevention and treatment of influenza. Influenza caused by oseltamivir-resistant viruses appears to be indistinguishable from illness caused by oseltamivir-sensitive viruses (*469*). When local viral surveillance data indicates that oseltamivir-resistant viruses are widespread in the community, clinicians have several options. Consultation with local health authorities to aid in decision-making is recommended as a first step. Persons who are candidates for receiving chemoprophylaxis as part of an outbreak known to be caused by oseltamivir-resistant viruses or who are being treated for influenza illness in communities where oseltamivir-resistant viruses are known to be circulating widely can receive zanamivir. However, zanamivir is not licensed for chemoprophylaxis indications in children aged <5 years, and is not licensed for treatment in children aged <7 years (*451*). In addition, zanamivir is not recommended for use in persons with chronic cardiopulmonary conditions, and can be difficult to administer to critically ill patients because of the inhalation mechanism of delivery. In these circumstances, a combination of oseltamivir and either rimantadine or amantadine can be considered, because influenza A (H1N1) viruses characterized to date that were resistant to oseltamivir have usually been susceptible to adamantane medications (CDC, unpublished data, 2008). However, adamantanes should not be used for chemoprophylaxis or treatment of influenza A unless they are part of a regimen that also includes a neuraminidase inhibitor, because viral surveillance data has documented that adamantane resistance among influenza A viruses is common. Influenza B viruses are not sensitive to adamantane drugs.

Control of Influenza Outbreaks in Institutions

Use of antiviral drugs for treatment and chemoprophylaxis of influenza is a key component of influenza outbreak control in institutions. In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccinations to unvaccinated staff and patients,

restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (*481--483*). Both adamantanes and neuraminidase inhibitors have been successfully used to control outbreaks caused by antiviral susceptible strains when antivirals are combined with other infection control measures. (*460,462,464,484--488*).

When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis with a neuraminidase inhibitor medication should be started as early as possible to reduce the spread of the virus (*489,490*). In these situations, having preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications. Specimens should be collected from ill cases for viral culture to assess antiviral resistance and provide data on the outbreak viruses. Chemoprophylaxis should be administered to all eligible residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 7--10 days after illness onset in the last patient (*489*). Chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk. Chemoprophylaxis should be considered for all employees, regardless of their vaccination status, if indications exist that the outbreak is caused by a strain of influenza virus that is not well-matched by the vaccine. Such indications might include multiple documented breakthrough influenza-virus infections among vaccinated persons, studies indicating low vaccine effectiveness, or circulation in the surrounding community of suspected index case(s) of strains not contained in the vaccine.

In addition to use in nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories, correctional facilities, or other settings in which persons live in close proximity). To limit the potential transmission of drug-resistant virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis.

Dosage

Dosage recommendations vary by age group and medical conditions (Table 4).

Adults

Zanamivir is licensed for treatment of adults with uncomplicated acute illness caused by influenza A or B virus, and for chemoprophylaxis of influenza among

adults. Zanamivir is not recommended for persons with underlying airways disease (e.g., asthma or chronic obstructive pulmonary diseases).

Oseltamivir is licensed for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for chemoprophylaxis of influenza among adults. Dosages and schedules for adults are listed (Table 4).

Children

Zanamivir is licensed for treatment of influenza among children aged ≥7 years. The recommended dosage of zanamivir for treatment of influenza is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart). Zanamivir is licensed for chemoprophylaxis of influenza among children aged ≥5 years; the chemoprophylaxis dosage of zanamivir for children aged ≥5 years is 10 mg (2 inhalations) once a day.

Oseltamivir is licensed for treatment and chemoprophylaxis among children aged ≥1 year. Recommended treatment dosages vary by the weight of the child: 30 mg twice a day for children who weigh ≤15 kg, 45 mg twice a day for children who weigh >15--23 kg, 60 mg twice a day for those who weigh >23--40 kg, and 75 mg twice a day for those who weigh >40 kg. Dosages for chemoprophylaxis are the same for each weight group, but doses are administered only once per day rather than twice.

Persons Aged ≥65 Years

No reduction in dosage for oseltamivir or zanamivir is recommended on the basis of age alone.

Persons with Impaired Renal Function

Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were reported (*450*). However, a limited number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose (*491,492*). On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function (*451*).

Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function (*450*). For patients with creatinine clearance of 10--30 mL per minute (*450*), a reduction of the treatment

dosage of oseltamivir to 75 mg once daily and in the chemoprophylaxis dosage to 75 mg every other day is recommended. No treatment or chemoprophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment.

Persons with Liver Disease

Use of zanamivir or oseltamivir has not been studied among persons with hepatic dysfunction.

Persons with Seizure Disorders

Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

Persons with Immunosuppression

A recent retrospective case-control study demonstrated that oseltamivir was safe and well tolerated when used during the control of an influenza outbreak among hematopoietic stem cell transplant recipients living in a residential facility (*493*).

Route

Oseltamivir is administered orally in capsule or oral suspension form. Zanamivir is available as a dry powder that is self-administered via oral inhalation by using a plastic device included in the package with the medication. Patients should be instructed about the correct use of this device.

Pharmacokinetics

Zanamivir

In studies of healthy volunteers, approximately 7%--21% of the orally inhaled zanamivir dose reached the lungs, and 70%--87% was deposited in the oropharynx (451,*494*). Approximately 4%--17% of the total amount of orally inhaled zanamivir is absorbed systemically. Systemically absorbed zanamivir has a half-life of 2.5--5.1 hours and is excreted unchanged in the urine. Unabsorbed drug is excreted in the feces (*451,465*).

Oseltamivir

Approximately 80% of orally administered oseltamivir is absorbed systemically (*495*). Absorbed oseltamivir is metabolized to oseltamivir carboxylate, the active neuraminidase inhibitor, primarily by hepatic esterases. Oseltamivir carboxylate has a half-life of 6--10 hours and is excreted in the urine by glomerular filtration

and tubular secretion via the anionic pathway (*450,496*). Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion (*468*).

Adverse Events

When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (Table 4); presence of other medical conditions; indications for use (i.e., chemoprophylaxis or therapy); and the potential for interaction with other medications.

Zanamivir

Limited data are available about the safety or efficacy of zanamivir for persons with underlying respiratory disease or for persons with complications of acute influenza, and zanamivir is licensed only for use in persons without underlying respiratory or cardiac disease (*497*). In a study of zanamivir treatment of ILI among persons with asthma or chronic obstructive pulmonary disease in which study medication was administered after use of a B2-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment (*451,498*). However, in a phase-I study of persons with mild or moderate asthma who did not have ILI, one of 13 patients experienced bronchospasm after administration of zanamivir (*451*). In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Because of the risk for serious adverse events and because efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying airway disease (*451*). Allergic reactions, including oropharyngeal or facial edema, also have been reported during postmarketing surveillance (*451,498*).

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and for those receiving placebo (i.e., inhaled lactose vehicle alone) (*428--432,498*). The most common adverse events reported by both groups were diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined (*451*). Zanamivir does not impair the immunologic response to TIV (*499*).

Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%) (*434,435*,*450,500*). Among children treated with oseltamivir, 14% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect (*437*), and a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (*450*). Similar types and rates of adverse events were reported in studies of oseltamivir chemoprophylaxis (*450*). Nausea and vomiting might be less severe if oseltamivir is taken with food (*450*). No published studies have assessed whether oseltamivir impairs the immunologic response to TIV.

Transient neuropsychiatric events (self-injury or delirium) have been reported postmarketing among persons taking oseltamivir; the majority of reports were among adolescents and adults living in Japan (*501*). FDA advises that persons receiving oseltamivir be monitored closely for abnormal behavior (*450*).

Use During Pregnancy

Oseltamivir and zanamivir are both "Pregnancy Category C" medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these two drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus; the manufacturers' package inserts should be consulted (*450,451*). However, no adverse effects have been reported among women who received oseltamivir or zanamivir during pregnancy or among infants born to such women.

Drug Interactions

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro and animal study data (*450,451,502*).

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of

oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate (*468*).

No published data are available concerning the safety or efficacy of using combinations of any of these influenza antiviral drugs. Package inserts should be consulted for more detailed information about potential drug interactions.

Sources of Information Regarding Influenza and Its Surveillance

Information regarding influenza surveillance, prevention, detection, and control is available at http://www.cdc.gov/flu. During October--May, surveillance information is updated weekly. In addition, periodic updates regarding influenza are published in *MMWR* (http://www.cdc.gov/mmwr). Additional information regarding influenza vaccine can be obtained by calling 1-800-CDC-INFO (1-800-232-4636). State and local health departments should be consulted about availability of influenza vaccine, access to vaccination programs, information related to state or local influenza activity, reporting of influenza outbreaks and influenza-related pediatric deaths, and advice concerning outbreak control.

Responding to Adverse Events After Vaccination

Health-care professionals should report all clinically significant adverse events after influenza vaccination promptly to VAERS, even if the health-care professional is not certain that the vaccine caused the event. Clinically significant adverse events that follow vaccination should be reported at http://www.vaers.hhs.gov. Reports may be filed securely online or by telephone at 1-800-822-7967 to request reporting forms or other assistance.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986, as amended, provides a mechanism through which compensation can be paid on behalf of a person determined to have been injured or to have died as a result of receiving a vaccine covered by VICP. The Vaccine Injury Table lists the vaccines covered by VICP and the injuries and conditions (including death) for which compensation might be paid. If the injury or condition is not on the Table, or does not occur within the specified time period on the Table, persons must prove that the vaccine caused the injury or condition.

For a person to be eligible for compensation, the general filing deadlines for injuries require claims to be filed within 3 years after the first symptom of the vaccine injury; for a death, claims must be filed within 2 years of the vaccine-related death and not more than 4 years after the start of the first symptom of the vaccine-related injury from which the death occurred. When a new vaccine is covered by VICP or when a new injury/condition is added to the Table, claims

that do not meet the general filing deadlines must be filed within 2 years from the date the vaccine or injury/condition is added to the Table for injuries or deaths that occurred up to 8 years before the Table change. Persons of all ages who receive a VICP-covered vaccine might be eligible to file a claim. Both the intranasal (LAIV) and injectable (TIV) trivalent influenza vaccines are covered under VICP. Additional information about VICP is available at http//www.hrsa.gov/vaccinecompensation or by calling 1-800-338-2382.

Reporting of Serious Adverse Events After Antiviral Medications

Severe adverse events associated with the administration of antiviral medications used to prevent or treat influenza (e.g., those resulting in hospitalization or death) should be reported to MedWatch, FDA's Safety Information and Adverse Event Reporting Program, at telephone 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or via the Internet by sending Report Form 3500 (available at http://www.fda.gov/medwatch/safety/3500.pdf). Instructions regarding the types of adverse events that should be reported are included on MedWatch report forms.

Additional Information Regarding Influenza Virus Infection Control Among Specific Populations

Each year, ACIP provides general, annually updated information regarding control and prevention of influenza. Other reports related to controlling and preventing influenza among specific populations (e.g., immunocompromised persons, HCP, hospital patients, pregnant women, children, and travelers) also are available in the following publications:

- CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2006;55(No. RR-15).
- CDC. Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-2).
- CDC. Recommended immunization schedules for persons aged 0--18 years---United States, 2007. MMWR 2008;57:Q1--4.
- CDC. Recommended adult immunization schedule---United States, October 2006--September 2007. MMWR 2006;55:Q1--4.
- CDC. Guidelines for preventing health-care--associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR 2003;53(No. RR-3).
- CDC. Respiratory hygiene/cough etiquette in health-care settings. Atlanta, GA: US Department of Health and Human Services, CDC; 2003. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm.
- CDC. Prevention and control of vaccine-preventable diseases in long-term care facilities. Atlanta, GA: US Department of Health and Human

Services, CDC; 2006. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/longtermcare.htm.
- Sneller V-P, Izurieta H, Bridges C, et al. Prevention and control of vaccine-preventable diseases in long-term care facilities. Journal of the American Medical Directors Association 2000;1(Suppl):S2--37.
- American College of Obstetricians and Gynecologists. Influenza vaccination and treatment during pregnancy. ACOG committee opinion no. 305. Obstet Gynecol 2004;104:1125--6.
- American Academy of Pediatrics. 2006 red book: report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006.
- Bodnar UR, Maloney SA, Fielding KL, et al. Preliminary guidelines for the prevention and control of influenza-like illness among passengers and crew members on cruise ships. Atlanta, GA: US Department of Health and Human Services, CDC; 1999. Available at http://www.cdc.gov/travel/CDCguideflufnl.PDF.
- CDC. General recommendations for preventing influenza A infection among travelers. Atlanta, GA: US Department of Health and Human Services, CDC; 2003. Available at http://www2.ncid.cdc.gov/travel/yb/utils/ybGet.asp?section=dis&obj=influenza.htm.
- CDC. Infection control guidance for the prevention and control of influenza in acute-care facilities. Atlanta, GA: US Department of Health and Human Services, CDC; 2007. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/health-carefacilities.htm.
- Food and Drug Administration. FDA Pandemic influenza preparedness strategic plan. Washington, DC: Food and Drug Administration; 2007. Available at http://www.fda.gov/oc/op/pandemic/strategicplan03_07.html.
- World Health Organization. Recommendations for influenza vaccines. Geneva, Switzerland: World Health Organization; 2007. Available at http://www.who.int/csr/disease/influenza/vaccinerecommendations/en/index.html.

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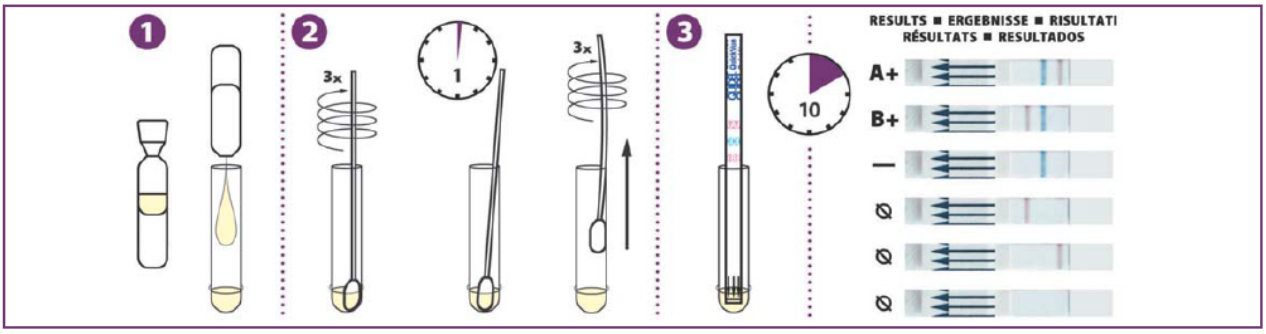
Universidad Veracruzana

ANEXO

QUICKVUE®
Influenza A+B TEST

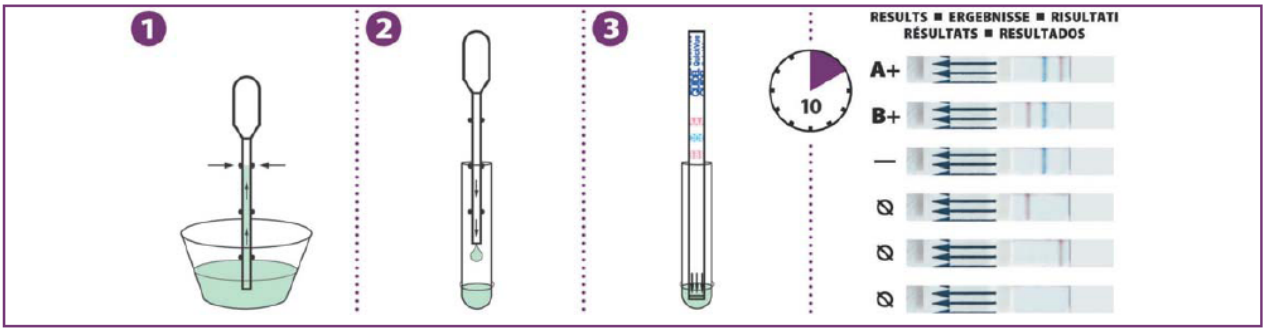
Nasal/Nasopharyngeal swab procedure:



Nasal Swab:
Sensitivity: A – 94%, B – 74%
Specificity: A – 90%, B – 97%
Accuracy: A – 91%, B – 93%
PV (+): A – 62%, B – 82%
PV (–): A – 99%, B – 95%

Nasopharyngeal Swab:
Sensitivity: A – 83%, B – 67%
Specificity: A – 89%, B – 98%
Accuracy: A – 88%, B – 95%
PV (+): A – 67%, B – 80%
PV (–): A – 95%, B – 96%

Nasal wash/aspirate procedure:



Fresh nasal wash/aspirate:
Sensitivity: A – 77%, B – 82%
Specificity: 99%
Accuracy: A – 95%, B – 96%
PV (+): A – 91%, B – 90%
PV (–): A – 96%, B – 97%

Frozen nasal wash:
Sensitivity: A – 86%
Specificity: A – 95%
Accuracy: A – 91%
PV (+): A – 93%
PV (–): A – 90%

****Test que ya se realiza en el laboratorio clínico del CESS**