

Transmission of MRSA Traced to Breast Milk

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WASHINGTON — Methicillin-resistant *Staphylococcus aureus* has been transmitted via breast milk, Dawn Terashita Gastelum, M.D., reported in a poster presentation at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. The two reported cases, which resulted in MRSA outbreaks in neonatal intensive care units at two Los Angeles hospitals,

suggest that hospital NICUs should consider screening mothers and family members for skin lesions at the time of delivery and obtaining breast milk cultures before infant feedings, said Dr. Terashita Gastelum of the Los Angeles County Department of Health Services.

The first case was in a premature (1,180 g at birth) quadruplet born to an Algerian mother who developed mastitis the day after delivery and was treated with dicloxacillin. Her breast milk was collected

3 days later and fed to the quadruplets and 12 days after that, the baby girl died of MRSA sepsis.

The bacterium subsequently was found in nasopharyngeal cultures of the mother, her three surviving infants, another infant in the NICU, and the mother's frozen postpartum breast milk samples. Molecular fingerprinting was identical for the four infants and the breast milk, but the mother's nasopharyngeal isolate was different.

"Since the mother was actually colonized by a different strain, it is unlikely that the infants obtained the MRSA during birth or through skin-to-skin contact. The breast milk is the only known source," Dr. Terashita Gastelum told FAMILY PRACTICE NEWS.

"It is easy to imagine that the macerated skin of the nipple on a postpartum woman is more susceptible to infection," she said at the conference, sponsored by the American Society for Microbiology.

The second case was an 1,199-g male infant born to an African American mother, who was fed her breast milk the day of birth and developed MRSA sepsis 8 days later. This mother had no sign of mastitis, but MRSA was cultured from her breast milk collected on the day of delivery. Four other infants from the NICU were also positive: two colonized and two infected. Isolates from the breast milk and the five cases were identical. ■

fluMist[®] Influenza Virus Vaccine Live, Intranasal

2004-2005 Formula
FOR NASAL ADMINISTRATION ONLY
Rx only
Brief summary of Prescribing Information
INDICATIONS AND USAGE

FluMist is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age.

FluMist is not indicated for immunization of individuals less than 5 years of age, or 50 years of age and older, or for therapy of influenza, nor will it protect against infections and illness caused by infectious agents other than influenza A or B viruses.

CONTRAINDICATIONS

Under no circumstances should FluMist[®] be administered parenterally.

Individuals with a history of hypersensitivity, especially anaphylactic reactions, to any component of FluMist, including eggs or egg products, should not receive FluMist.

FluMist is contraindicated in children and adolescents (5-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye syndrome with aspirin and wild-type influenza infection.

FluMist should not be administered to individuals who have a history of Guillain-Barré syndrome.

As with other live virus vaccines, FluMist should not be administered to individuals with known or suspected immune deficiency diseases such as combined immunodeficiency, agammaglobulinemia, and thymic abnormalities and conditions such as human immunodeficiency virus infection, malignancy, leukemia, or lymphoma. FluMist is also contraindicated in patients who may be immunosuppressed or have altered or compromised immune status as a consequence of treatment with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies.

WARNINGS

The safety of FluMist in individuals with asthma or reactive airways disease has not been established. In a large safety study in children 1-17 years of age, children <5 years of age who received FluMist were found to have an increased rate of asthma within 42 days of vaccination when compared to placebo recipients (see ADVERSE REACTIONS). FluMist should not be administered to individuals with a history of asthma or reactive airways disease.

The safety of FluMist in individuals with underlying medical conditions that may predispose them to severe disease following wild-type influenza infection has not been established. FluMist is not indicated for these individuals. High-risk individuals include, but are not limited to, adults and children with chronic disorders of the cardiovascular and pulmonary systems, including asthma; pregnant women; adults and children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes), renal dysfunction, or hemoglobinopathies; and adults and children with congenital or acquired immunosuppression caused by underlying disease or immunosuppressive therapy (see CONTRAINDICATIONS). Intramuscularly administered inactivated influenza vaccines are available to immunize high-risk individuals.

As with any vaccine, FluMist may not protect 100% of individuals receiving the vaccine.

PRECAUTIONS

General: CARE IS TO BE TAKEN BY THE HEALTH CARE PROVIDER FOR THE SAFE AND EFFECTIVE USE OF THIS PRODUCT.

Prior to administration of FluMist, individuals or their parent/guardian should be asked about their current health status and their personal medical history, including immune status, to determine the existence of any contraindications (see CONTRAINDICATIONS and WARNINGS) to immunization with FluMist. FluMist recipients should avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days. EPINEPHRINE INJECTION (1:1000) OR COMPARABLE TREATMENT MUST BE READILY AVAILABLE IN THE EVENT OF AN ACUTE ANAPHYLACTIC REACTION FOLLOWING VACCINATION. The health care provider should ensure prevention of any allergic or other adverse reactions by reviewing the individual's history for possible sensitivity to influenza vaccine components, including eggs and egg products. Administration of FluMist should be postponed until after the acute phase (at least 72 hours) of febrile and/or respiratory illnesses.

Information for Vaccine Recipients or Parents/Guardians: Vaccine recipients or their parents/guardians should be informed by the health care provider of the potential benefits and risks of FluMist, and the need for two doses for the first use of FluMist in 5-8 year olds. Due to the possible transmission of vaccine virus, vaccine recipients or their parents/guardians should be advised to avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days. The vaccine recipient or the parent/guardian accompanying the vaccine recipient should be told to report any suspected adverse events to the physician or clinic where the vaccine was administered (see ADVERSE EVENT REPORTING).

Drug Interactions: Children or adolescents who are receiving aspirin therapy or aspirin-containing therapy should not receive FluMist (see CONTRAINDICATIONS). FluMist should not be administered to persons on immunosuppressive therapy. The concurrent use of FluMist with antiviral compounds that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for interference between such compounds and FluMist, it is advisable not to administer FluMist until 48 hours after the cessation of antiviral therapy and that antiviral agents not be administered until two weeks after administration of FluMist unless medically indicated.

There are no data regarding co-administration of FluMist with other intranasal preparations, including steroids.

Concurrent Administration with Other Vaccines: The safety and immunogenicity of FluMist when administered concurrently with other vaccines have not been determined. Therefore, FluMist should not be administered concurrently with other vaccines. Studies of FluMist in healthy individuals excluded subjects who received any live virus vaccine within one month of enrollment and any inactivated or subunit vaccine within two weeks of enrollment; therefore, health care providers should adhere to these intervals when administering FluMist.

Laboratory Interactions: Data related to the length of time that FluMist can be recovered from nasal specimens of children and adults are limited. Nasopharyngeal secretions or swabs collected from vaccinees may test positive for influenza virus for up to three weeks.

Carcinogenesis, Mutagenesis, Impairment of Fertility: FluMist has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

Pregnancy (Category C): Animal reproduction studies have not been conducted with FluMist. It is also not known whether FluMist can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Therefore, FluMist should not be administered to pregnant women.

Nursing Mothers: It is not known whether FluMist is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if FluMist is administered to nursing mothers.

Pediatric Use: The safety of FluMist in infants and children <60 months of age has not been established.

Geriatric Use: Clinical studies with FluMist did not include sufficient numbers of adults age 65 years and older to determine if they respond differently from younger individuals. The safe use of FluMist in persons 65 years and older has not been established.

ADVERSE REACTIONS

Serious Adverse Events: Across all clinical trials, serious adverse events (SAEs) were monitored after vaccination for 42 days in children and for 28 days in adults. SAEs occurred at a similar rate (<1%) in FluMist and placebo recipients for both healthy children and healthy adults.

Overall, across the placebo-controlled trials in adults and children, the incidence of selected adverse reactions that may be complications of influenza (such as pneumonia, bronchitis, bronchiolitis, or central nervous system events) was similar in FluMist and placebo groups.

Adverse Events in Placebo-Controlled Trials: In all placebo-controlled studies, allantoic fluid from uninfected eggs was used as the placebo. In randomized, placebo-controlled trials, 4719 healthy children aged 5-17 years and 2864 healthy adults 18-49 years of age received FluMist and 2327 healthy children and 1454 healthy adults received the placebo. In placebo-controlled clinical trials conducted in healthy populations, solicited adverse events and daily temperatures were collected on diary cards. These solicited events included runny nose/nasal congestion, sore throat, cough, irritability, headache, chills, vomiting, muscle aches, and decreased activity and a feeling of tiredness/weakness.

Solicited Adverse Events in Children: Table 1 shows an analysis of solicited events for the Pediatric Efficacy Study in the subset of healthy children 60-71 months of age. The largest absolute differences between FluMist and placebo after Dose One were observed in the incidences of headache and runny nose/nasal congestion. No differences were observed for fever (>100°F oral). Following Dose Two, the largest absolute differences between FluMist and placebo were runny nose/nasal congestion and cough. There was no significant increase in influenza-like illness (ILI) as defined by the CDC in the FluMist group compared to the placebo group. CDC has defined CDC-ILI as having fever (temperature $\geq 100^\circ\text{F}$ oral) plus either cough or sore throat on the same day or on consecutive days.

Table 1: Summary of Solicited Events Observed within 10 Days after Each Dose for Vaccine and Placebo Recipients; Healthy Children 60-71 Months of Age

Event	Post-Dose One		Post-Dose Two	
	FluMist 214*	Placebo 95*	FluMist 161*	Placebo 75*
Any event	65.4	61.4	66.5	53.3
Cough	26.8	32.7	38.5	30.7
Runny Nose/Nasal Congestion	48.1	44.2	46.0	32.0
Sore Throat	12.6	19.8	9.3	16.0
Irritability	19.5	16.8	9.9	9.3
Headache	17.8	11.6	6.8	16.0
Chills	6.1	5.3	2.5	4.0
Vomiting	4.7	3.2	5.6	12.0
Muscle Aches	6.1	4.2	5.0	4.0
Decreased Activity	14.0	12.6	10.6	13.3
Fever [†] :				
Temp 1	9.5	9.9	4.3	4.0
Temp 2	2.2	2.0	0.6	1.3
Temp 3	0.0	0.0	0.0	0.0

Note: There were no statistically significant differences in any of these events (p-value >0.05); Fisher's exact method.

* Number of evaluable subjects (those who returned diary cards) for each event.

[†] Fever:

Temp 1: Oral >100°F, rectal or axillary >100.6°F, or axillary >99.6°F.

Temp 2: Oral >102°F, rectal or axillary >102.6°F, or axillary >101.6°F.

Temp 3: Oral >104°F, rectal or axillary >104.6°F, or axillary >103.6°F.

For the cohort of 128 children who received FluMist[®] (Influenza Virus Vaccine Live, Intranasal) across three consecutive years, rates of solicited adverse events were not significantly increased when compared to placebo recipients.

Medically Attended Events in Children and Adolescents: A large randomized, double-blind, placebo-controlled trial in healthy children 1 through 17 years of age was conducted at 31 clinics in the Northern California Kaiser-Permanente Health Maintenance Organization (HMO) to assess the rate of medically attended events (MAEs) within 42 days of vaccination. Participants were randomized 2:1 (vaccine:placebo). A total of 6657 evaluable children 5-17 years of age were enrolled, including 3244 boys and 3413 girls. Of these 6657 children, 2606 were 5-8 years of age and 4051 were 9-17 years of age. Dose Two for children less than nine years of age was to be administered 28 to 42 days after Dose One.

Data regarding MAEs were obtained from the Kaiser-Permanente computerized health care utilization databases for hospitalizations, emergency department visits and clinical visits. MAEs were analyzed individually and within four pre-specified grouped diagnoses: acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza. For these four pre-specified grouped diagnoses, no significant increase in risk for FluMist recipients was seen in the combined analyses across all utilization settings, doses, and age groups. Selected respiratory tract illnesses of special interest (pneumonia, bronchitis, bronchiolitis, and croup) were included in acute respiratory tract events and were not associated with increased risk for FluMist recipients in any protocol-specified analysis. No systemic bacterial infection occurred. In FluMist recipients, an increased risk was not observed for rare events that have been reported with naturally occurring influenza virus infection, including seizures, febrile seizures, and epilepsy. No cases of encephalitis, acute filoplastic polyneuritis (Guillain-Barré syndrome), Reye syndrome, or myocarditis (influenza-associated rare disorders) were reported in this study.

In this study, in individuals 5-17 years of age, for individual MAEs were significantly increased and 11 were significantly decreased. Of the four individual MAEs associated with increased risk, a biological association with FluMist is plausible for one: abdominal pain. Of the 11 individual MAEs associated with decreased risk, a biologically plausible association with FluMist exists for seven: asthma, bronchitis, conjunctivitis, cough, viral syndrome, otitis media, and wheezing/shortness of breath. However, in the same study, a statistically significant increase in asthma or reactive airways disease was observed for children 12-59 months of age following Dose One (Relative Risk 3.53, 90% CI: 1.1, 11.7). As a result of this finding, FluMist is not indicated for children <60 months of age.

Solicited Adverse Events in Adults: In the placebo-controlled Adult Effectiveness Study, the rate of solicited adverse events in the subset of healthy adults 18-49 years of age are shown in Table 2. Statistically significant differences were observed for any event, cough, runny nose, sore throat, chills, and tiredness/weakness. Fever >100°F was similar in FluMist and placebo recipients after a single dose. There was no significant increase in ILI as defined by the CDC in the FluMist group compared to the placebo group.

Table 2: Summary of Solicited Events Observed within 7 Days after Each Dose for Vaccine and Placebo Recipients; Healthy Adults 18-49 Years of Age

Event	FluMist N=2548*	Placebo N=1290*
Any event	71.9*	62.6
Cough	13.9*	10.8
Runny Nose	44.8*	27.1
Sore Throat	27.8*	17.1
Headache	40.4	38.4
Chills	8.6*	6.0
Muscle Aches	16.7	14.6
Tiredness/Weakness	25.7*	21.6
Fever [†] :		
Oral Temp >100°F	1.5	1.3
Oral Temp >101°F	0.5	0.7
Oral Temp >102°F	0.1	0.2
Oral Temp >103°F	0.0	0.0

* Denotes statistically significant p-value [†]0.05; no adjustments for multiple comparisons; Fisher's exact method.

[†] Number of evaluable subjects (those who returned diary cards). [97.9% of FluMist recipients and 97.9% of placebo recipients.]

Other Adverse Events in Children and Adults: In addition to the solicited events, parents of subjects in the Pediatric Efficacy Trial also reported other adverse events that occurred during the course of the trial. Among healthy children age 60-71 months, the events that occurred in at least 1% of FluMist recipients and at a higher rate compared to placebo were: abdominal pain (3.7% FluMist vs 0% placebo), otitis media (1.4% FluMist vs 0% placebo), accidental injury (2.3% FluMist vs 2.1% placebo), diarrhea (3.7% FluMist vs 1.1% placebo), following Dose One and otitis media (3.1% FluMist vs 1.3% placebo) following Dose Two. None of these differences were statistically significant. In addition to the solicited events, adults who participated in the Adult Effectiveness Study also reported other adverse events that occurred during the course of the clinical trial. For adults 18-49 years of age in the Adult Effectiveness Study, nasal congestion (9.2% FluMist vs 2.2% placebo), rhinitis (6.3% FluMist vs 3.1% placebo), and sinusitis (4.1% FluMist vs 2.2% placebo) were reported significantly more often by FluMist recipients compared to placebo recipients. Adverse events reported post-licensure have included nausea, rash, hypersensitivity reactions (including anaphylaxis, facial edema, and urticaria). These events occurred at similar rates in FluMist vs placebo recipients in pre-licensure studies.

Annually, 20-40 cases of Guillain-Barré syndrome (GBS) that occur within 42 days of administration of inactivated influenza vaccine are reported to VAERS. In 2003-2004, one case of GBS with temporal association with FluMist was reported. Evidence of a causal relationship between influenza vaccines, including FluMist, has not been established.

ADVERSE EVENT REPORTING

Reporting by vaccine recipients or the parents/guardians of vaccinees and health care providers of all adverse events occurring after vaccine administration is encouraged. The U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the FDA Web site at: <http://www.vaers.org>.

DOSE AND ADMINISTRATION

FOR NASAL USE ONLY. DO NOT ADMINISTER PARENTERALLY.

FluMist[®] should be administered according to the following schedule:

Age Group	Vaccination Status	Dosage Schedule
Children age 5 years through 8 years	Not previously vaccinated with FluMist	2 doses (0.5 mL each, 60 days apart \pm 14 days) for initial season
Children age 5 years through 8 years	Previously vaccinated with FluMist	1 dose (0.5 mL) per season
Children and Adults age 9 through 49 years	Not applicable	1 dose (0.5 mL) per season

For healthy children age 5 years through 8 years who have not previously received FluMist vaccine, the recommended dosage schedule for nasal administration is one 0.5 mL dose followed by a second 0.5 mL dose given at least 6 weeks later. Only limited data are available on the degree of protection in children who receive one dose.

For all other healthy individuals, including children age 5-8 years who have previously received at least one dose of FluMist, the recommended schedule is one dose.

FluMist should be administered prior to exposure to influenza. The peak of influenza activity is variable from year to year, but generally occurs in the U.S. between late December and early March. Because the duration of protection induced by FluMist is not known and yearly antigenic variation in the influenza strains is possible, annual revaccination may increase the likelihood of protection.

Based on FluMist Prescribing Information dated September 2004.

140 L.A. Children Hospitalized With MRSA in 6 Months

WASHINGTON — A clonal outbreak of community-acquired methicillin-resistant *Staphylococcus aureus* in Los Angeles County led to a high rate of hospitalizations among children in 2003, Elizabeth Bancroft, M.D., reported in a poster at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Following skin infection outbreaks of MRSA (USA 300; ST:8) in 2002, community-acquired methicillin-resistant *S. aureus* (CAMRSA) infections in hospitalized children less than 18 years of age was made a reportable condition from May 5 to Nov. 7, 2003. A total of 140 cases were reported between those dates, said Dr. Bancroft of the Los Angeles County Department of Health Services.

Mean age of the children was 6.25 years (range 0-17), 51% were female, 66% were Hispanic, 16% white, 15% black, and the remainder said they were "other." Their mean length of stay was 5.13 days (range 1-30). Diagnoses included cellulitis in 44%, abscess in 36%, and a combination of the two in 11%.

Prior misdiagnosis as insect or spider bites occurred in 23%, and 75% of those who had been treated with antibiotics were initially treated inappropriately with β -lactams, she said.

Among 82 for whom a caregiver was interviewed, 24 (29%) had household contact with a skin infection within a month of the child's infection. Other nosocomial risk factors were present in 29 (35%), while risk factors for community-acquired infection were present in 38 (46%), including 9 (11%) who had contact with a recently incarcerated person.

Of 83 isolates analyzed, 79 (96%) were consistent with the USA 300; ST:8 CAMRSA genotype, even though many of the children had nosocomial risk factors.

—Miriam E. Tucker

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