

# Blood Lead Levels Linked to Osteoarthritis Severity

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PRAGUE — Blood lead levels significantly below those that are defined as toxic by the Centers for Disease Control and Prevention are associated with increased rates of moderate to severe knee osteoarthritis, reported Dr. Joanne M. Jordan, associate director of the Thurston Arthritis Research Center at the University of North Carolina, Chapel Hill.

“Essentially this is subclinical lead toxicity,” she said in an interview at the 2006 World Congress on Osteoarthritis. “This may be a new, potentially modifiable risk factor for osteoarthritis.”

In a cohort of 790 subjects, mean age 60 years, taken from the Johnston County Osteoarthritis Project Metals Exposure study, Dr. Jordan found that blood lead levels were not associated with the presence of osteoarthritis (OA), but they were associated with severity of the condition.

The subjects had a mean lead level of 2.0 mcg/dL, with most being well below the level of 10.0 mcg/dL that the CDC considers toxic, she said. After adjustment for age, gender, race, education, body mass index, current alcohol use, and current smoking status, the study found that subjects with blood lead levels in the highest quintile had a significant 30% greater chance of having moderate to severe knee OA, compared with subjects in the lowest quintile, she reported at the congress,

which was sponsored by the Osteoarthritis Research Society International. Additionally, those in the highest quintile also had a 60% greater chance of having bilateral knee OA—although this difference did not reach statistical significance.

In general, blood lead levels were higher in older subjects, and in African Americans compared with whites. Additionally,



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DR. JORDAN

there were higher lead levels in men compared with women, in subjects with less education compared with those who had more education, and in current alcohol users and smokers compared with abstainers.

Roughly 95% of the body’s lead burden is stored in bone, and this store contributes 65% to blood lead levels, said Dr. Jordan. With a half-life of decades, bone and blood lead interfere with the uptake of dietary calcium and vitamin D.

## Vitamin D Intake In Women Tied To Knee Arthritis

PRAGUE — Low dietary vitamin D intake is linked to an increased rate of knee osteoarthritis, Dr. Nigel K. Arden reported at the 2006 World Congress on Osteoarthritis.

The association was seen in tibiofemoral but not patellofemoral disease, and in women but not in men, Dr. Arden said at the meeting, which was sponsored by the Osteoarthritis Research Society International.

“This effect was driven by dietary intake, not supplementation,” he added, noting that the mean dietary vitamin D intake in the 957 British patients, measured by food frequency questionnaires, was 3.2 mcg per day. A total of 39% of the cohort took vitamin D supplements, boosting their daily intake to 4.3 mcg per day, which is still “woefully below what’s recommended,” said Dr. Arden of the University of Southampton (England).

The study randomized patients from the larger Hertfordshire Cohort Study, a multiple outcome study which included patients born in Hertfordshire, England, from 1931 to 1939 and still living there. It noted a 10.5% rate of symptomatic, radiographic tibiofemoral OA in the cohort at baseline; this was negatively associated with dietary vitamin D intake.

While vitamin D insufficiency is known to increase with age, it is expected to increase more significantly with the growing emphasis on sun avoidance and the use of sunscreen, Dr. Arden said.

—Kate Johnson

## Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine Menactra®

FOR INTRAMUSCULAR INJECTION

Brief Summary: Please consult package insert for full prescribing information.

### INDICATIONS AND USAGE

Menactra vaccine is indicated for active immunization of adolescents and adults 11–55 years of age for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135.

Menactra vaccine is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroup B.

Menactra vaccine is not indicated for treatment of meningococcal infections.

Menactra vaccine is not indicated for immunization against diphtheria.

The Advisory Committee on Immunization Practices (ACIP) has published recommendations for the prevention and control of meningococcal disease in the US (refer to www.cdc.gov).<sup>1</sup>

As with any vaccine, Menactra vaccine may not protect 100% of individuals.

### CONTRAINDICATIONS

Known hypersensitivity to any component of Menactra vaccine including diphtheria toxoid, or a life-threatening reaction after previous administration of a vaccine containing similar components,<sup>2</sup> are contraindications to vaccine administration.

Known history of Guillain-Barré Syndrome (see WARNINGS section) is a contraindication to vaccine administration.

Known hypersensitivity to dry natural rubber latex (see WARNINGS section) is a contraindication to vaccine administration.

### WARNINGS

Guillain-Barré Syndrome (GBS) has been reported in temporal relationship following administration of Menactra vaccine (see ADVERSE REACTIONS, POST-MARKETING REPORTS section). Persons previously diagnosed with GBS should not receive Menactra vaccine.

The stopper of the vial contains dry natural rubber latex, which may cause allergic reactions in latex-sensitive individuals.

Because of the risk of hemorrhage, Menactra vaccine should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer Menactra vaccine in such persons, it should be given with caution, with steps taken to avoid the risk of bleeding or hematoma formation following injection.

The ACIP has published guidelines for vaccination of persons with recent or acute illness (refer to www.cdc.gov).<sup>3</sup>

### PRECAUTIONS

#### GENERAL

Before administration, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient’s previous immunization history, the presence of any contraindications to immunization, the current health status, and history concerning possible sensitivity to the vaccine, similar vaccine, or to latex.

AS A PRECAUTIONARY MEASURE, EPINEPHRINE INJECTION (1:1000) AND OTHER APPROPRIATE AGENTS AND EQUIPMENT MUST BE IMMEDIATELY AVAILABLE IN CASE OF ANAPHYLACTIC OR SERIOUS ALLERGIC REACTIONS.

As part of the patient’s immunization record, the date, lot number and manufacturer of the vaccine administered should be recorded. Special care should be taken to avoid injecting the vaccine subcutaneously since clinical studies have not been conducted to establish safety and efficacy of the vaccine using this route of administration.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of blood borne infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazardous waste guidelines.

The immune response to Menactra vaccine administered to immunosuppressed persons has not been studied.

#### INFORMATION FOR PATIENTS

Prior to administration of Menactra vaccine, the health-care professional should inform the patient, parent, guardian, or other responsible adult of the potential benefits and risks to the patient, and provide vaccine information statements (see ADVERSE REACTIONS and WARNINGS sections). Patients, parents or guardians should be instructed to report any suspected adverse reactions to their health-care professional. Females of childbearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy registry to monitor fetal outcomes of pregnant women exposed to Menactra vaccine. If they are pregnant or become aware they were pregnant at the time of Menactra vaccine immunization, they should contact their health-care professional or Sanofi Pasteur Inc. at 1-800-822-2463 (see PRECAUTIONS section).

#### DRUG INTERACTION

For information regarding concomitant administration of Menactra vaccine with other vaccines, refer to ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines.

#### CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Menactra vaccine has not been evaluated in animals for its carcinogenic or mutagenic potentials or for impairment of fertility.

#### PREGNANCY CATEGORY C

Animal reproduction studies were performed in mice using 0.2 mL of Menactra vaccine (900 times the human dose, adjusted by body weight). There were no effects on fertility, maternal health, embryo/fetal survival, or post-natal development. Skeletal examinations revealed one fetus (1 of 234 examined) in the vaccine group with a cleft palate. None were observed in the concurrent control group (0 of 174 examined). There are no data that suggest that this isolated finding is vaccine related, and no other skeletal and organ malformations were observed in this study. There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, Menactra vaccine should be used during pregnancy only if clearly needed. Health-care providers are encouraged to register pregnant women who receive Menactra vaccine in Sanofi Pasteur Inc.’s vaccination pregnancy registry by calling 1-800-822-2463.

#### NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Menactra vaccine is administered to a nursing woman.

#### PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF MENACTRA VACCINE IN CHILDREN BELOW THE AGE OF 11 YEARS HAVE NOT BEEN ESTABLISHED.

#### GERIATRIC USE

SAFETY AND EFFECTIVENESS OF MENACTRA VACCINE IN ADULTS OLDER THAN 55 YEARS HAVE NOT BEEN ESTABLISHED.

#### ADVERSE REACTIONS

The safety of Menactra vaccine was evaluated in 6 clinical studies that enrolled 7642 participants aged 11–55 years who received Menactra vaccine and 3041 participants who received Menomune-AC/Y/W-135 vaccine. There were no substantive differences in demographic characteristics between the vaccine groups. Among Menactra vaccine recipients of all ages, 21.3%, 53.2% and 25.5% were in the 11–14, 15–25 and 26–55-year age groups, respectively. Among Menomune-AC/Y/W-135 vaccine recipients of all ages, 16.1%, 51.9% and 32.0% were in the 11–14, 15–25 and 26–55-year age groups, respectively.

The two primary safety studies were randomized, active-controlled trials that enrolled participants 11–18 years of age (Menactra vaccine, N=2270; Menomune-AC/Y/W-135 vaccine, N=972) and 18–55 years of age (Menactra vaccine, N=1384; Menomune-AC/Y/W-135 vaccine, N=1170), respectively. As the route of administration differed for the two vaccines (Menactra vaccine given intramuscularly, Menomune-AC/Y/W-135 given subcutaneously), study personnel collecting the safety data differed from personnel administering the vaccine. Solicited local and systemic reactions were monitored daily for 7 days post-vaccination using a diary card. Participants were monitored for 28 days for unsolicited adverse events and for 6 months post-vaccination for visits to an emergency room, unexpected visits to an office physician, and serious adverse events. Unsolicited adverse event information was obtained either by telephone interview or at an interim clinic visit. Information regarding adverse events that occurred in the 6-month post-vaccination time period was obtained via a scripted telephone interview. At least 94% of participants from the two studies completed the 6-month follow-up evaluation.

In the two concomitant vaccination studies with Menactra and either Typhim Vi or Td vaccines, local and systemic adverse events were monitored for 7 days post vaccination using a diary card. Serious adverse events occurring within 1 month after each vaccination were reported and recorded.

#### SERIOUS ADVERSE EVENTS IN ALL SAFETY STUDIES

Serious adverse events reported within a 6-month time period following vaccination occurred at the same rate (1.3%) in the Menactra vaccine and Menomune-AC/Y/W-135 vaccine groups. The events reported were consistent with events expected in healthy adolescent and adult populations.

#### SOLICITED ADVERSE EVENTS IN THE PRIMARY SAFETY STUDIES

The most commonly reported solicited adverse reactions in adolescents, ages 11–18 years (TABLE 1), and adults, ages 18–55 years (TABLE 2), were local pain, headache and fatigue. Except for redness in adults, local reactions were more frequently reported after Menactra vaccination than after Menomune-AC/Y/W-135 vaccination. The majority of local and systemic reactions following Menactra or Menomune-AC/Y/W-135 vaccination were reported as mild in intensity. No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the vaccine groups.

TABLE 1: PERCENTAGE OF PARTICIPANTS 11–18 YEARS OF AGE REPORTING SOLICITED REACTIONS

Reaction	Menactra vaccine			Menomune-AC/Y/W-135 vaccine		
	Any	Moderate	Severe	Any	Moderate	Severe
Redness†	10.9*	1.6*	0.6*	5.7	0.4	0.0
Swelling†	10.8*	1.9*	0.5*	3.6	0.3	0.0
Induration†	15.7*	2.5*	0.3	5.2	0.5	0.0
Pain†	59.2*	12.8*	0.3	28.7	2.6	0.0
Headache§	35.6*	9.6*	1.1	29.3	6.5	0.4
Fatigue§	30.0*	7.5	1.1*	25.1	6.2	0.2
Malaise§	21.9*	5.8*	1.1	16.8	3.4	0.4
Arthralgia§	17.4*	3.6*	0.4	10.2	2.1	0.1
Diarrhea¶	12.0	1.6	0.3	10.2	1.3	0.0
Anorexia¶	10.7*	2.0	0.3	7.7	1.1	0.2
Chills¶	7.0*	1.7*	0.2	3.5	0.4	0.1
Fever¶	5.1*	0.6	0.0	3.0	0.3	0.1
Vomiting**	1.9	0.4	0.3	1.4	0.5	0.3
Rash††	1.6			1.4		
Seizure†††	0.0			0.0		

\* Denotes  $p < 0.05$  level of significance. The  $p$  values were calculated for each category and severity using Chi Square test; † Moderate: 1.0–2.0 inches, Severe:  $> 2.0$  inches; ‡ Moderate: interferes with normal activities, Severe: Disabling, unwilling to move arm; § Severe: Requiring bed rest; ¶ Severe:  $\geq 5$  episodes; † Severe: skipped  $\geq 3$  meals; † Severe:  $\geq 39.5^\circ\text{C}$ ; \*\* Severe:  $\geq 3$  episodes; †† These solicited adverse events were reported as present or absent only.

TABLE 2: PERCENTAGE OF PARTICIPANTS 18–55 YEARS OF AGE REPORTING SOLICITED REACTIONS

Reaction	Menactra vaccine			Menomune-AC/Y/W-135 vaccine		
	Any	Moderate	Severe	Any	Moderate	Severe
Redness†	14.4	2.9	1.1*	16.0	1.9	0.1
Swelling†	12.6*	2.3*	0.9*	7.6	0.7	0.0
Induration†	17.1*	3.4*	0.7*	11.0	1.0	0.0
Pain†	53.9*	11.3*	0.2	48.1	3.3	0.1
Headache§	41.4	10.1	1.2	41.8	8.9	0.9
Fatigue§	34.7	8.3	0.9	32.3	6.6	0.4
Malaise§	23.6	6.6*	1.1	22.3	4.7	0.9
Arthralgia§	19.8*	4.7*	0.3	16.0	2.6	0.1
Diarrhea¶	16.0	2.6	0.4	14.0	2.9	0.3
Anorexia¶	11.8	2.3	0.4	9.9	1.6	0.4
Chills¶	9.7*	2.1*	0.6*	5.6	1.0	0.0
Fever¶	1.5*	0.3	0.0	0.5	0.1	0.0
Vomiting**	2.3	0.4	0.2	1.5	0.2	0.4
Rash††	1.4			0.8		
Seizure†††	0.0			0.0		

\* Denotes  $p < 0.05$  level of significance. The  $p$  values were calculated for each category and severity using Chi Square test; † Moderate: 1.0–2.0 inches, Severe:  $> 2.0$  inches; ‡ Moderate: interferes with normal activities, Severe: Disabling, unwilling to move arm; § Severe: Requiring bed rest; ¶ Severe:  $\geq 5$  episodes; † Severe: skipped  $\geq 3$  meals; † Severe:  $\geq 40.0^\circ\text{C}$ ; \*\* Severe:  $\geq 3$  episodes; †† These solicited adverse events were reported as present or absent only.

#### ADVERSE EVENTS IN CONCOMITANT VACCINE STUDIES

Local and Systemic reactions when given with Td vaccine

The two vaccine groups reported similar frequencies of local pain, induration, redness and swelling at the Menactra injection site, as well as, at the Td injection site. Pain was the most frequent local reaction reported at both the Menactra and Td injection sites. More participants experienced pain after Td vaccination than after Menactra vaccination (71% versus 53%). The majority (66%–77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination.

The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra vaccine was administered 28 days after Td. In both groups, the most common reactions were headache (Menactra vaccine + Td, 36%; Td + Placebo, 34%; Menactra vaccine alone, 22%) and fatigue (Menactra vaccine + Td, 32%; Td + Placebo, 29%; Menactra vaccine alone, 17%). No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the groups. Fever  $\geq 40.0^\circ\text{C}$  occurred at  $\leq 0.5\%$  in all groups. No seizures occurred in either group.

Local and Systemic Reactions when Given with Typhim Vi Vaccine

The two vaccine groups reported similar frequencies of local pain, induration, redness and swelling at the Menactra injection site, as well as, at the Typhim Vi injection site. Pain was the most frequent local reaction reported at both the Menactra and Typhim Vi injection sites. More participants experienced pain after Typhim Vi vaccination than after Menactra vaccination (76% versus 47%). The majority (70%–77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache (Menactra + Typhim Vi vaccine, 41%; Typhim Vi vaccine + Menactra, 42%; Menactra vaccine alone, 33%) and fatigue (Menactra + Typhim Vi vaccine, 38%; Typhim Vi vaccine + Placebo, 35%; Menactra vaccine alone, 27%). No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the groups. Fever  $\geq 40.0^\circ\text{C}$  and seizures were not reported in either group.

#### POST-MARKETING REPORTS

The following adverse events have been reported during post-approval use of Menactra vaccine. Because these events were reported voluntarily from a population of uncertain size, it is not always possible to reliably calculate their frequency or to establish a causal relationship to Menactra vaccine exposure.

Nervous system disorders - Guillain-Barré Syndrome, transverse myelitis

#### DOSAGE AND ADMINISTRATION

Menactra vaccine should be administered as a single 0.5 mL injection by the intramuscular route, preferably in the deltoid region. Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Do not administer this product intravenously, subcutaneously, or intradermally.

The need for, or timing of, a booster dose of Menactra vaccine has not yet been determined.

Parenteral drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

#### CONCOMITANT ADMINISTRATION WITH OTHER VACCINES

Safety and immunogenicity data are available on concomitant administration of Menactra vaccine with Typhim Vi, and Td vaccines (see ADVERSE REACTIONS section). Concomitant administration of Menactra vaccine with Td did not result in reduced tetanus, diphtheria or meningococcal antibody responses compared with Menactra vaccine administered 28 days after Td.<sup>4</sup> However, for meningococcal serogroups C, Y and W-135, bactericidal antibody titers (GMTs) and the proportion of participants with a 4-fold or greater rise in Serum Bactericidal Assay (SBA) using baby rabbit complement (SBA-BR) titer were higher when Menactra vaccine was given concomitantly with Td than when Menactra vaccine was given one month following Td. The clinical relevance of these findings has not been fully evaluated.<sup>4</sup>

Concomitant administration of Menactra vaccine with Typhim Vi vaccine did not result in reduced antibody responses to any of the vaccine antigens.<sup>4</sup>

The safety and immunogenicity of concomitant administration of Menactra vaccine with vaccines other than Typhim Vi or Td vaccines have not been determined.

Menactra vaccine must not be mixed with any vaccine in the same syringe. Therefore, separate injection sites and different syringes should be used in case of concomitant administration.

#### STORAGE

Store between  $2^\circ\text{C}$  to  $8^\circ\text{C}$  ( $35^\circ\text{F}$  to  $46^\circ\text{F}$ ). DO NOT FREEZE. Product that has been exposed to freezing should not be used. Protect from light. Do not use after expiration date.

REFERENCES: 1. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Prevention and Control of Meningococcal Disease and Meningococcal Disease and College Students. MMWR 2000;49(RR-7). 2. Ball R, et al. Safety Data on Meningococcal Polysaccharide Vaccine from the Vaccine Adverse Event Reporting System. CID 2001;32:1273-1280. 3. ACIP. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR02):1-36. 4. Data on file, Aventis Pasteur Inc. – 092503.

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