

# PCV7 Vaccine Tied to Rise in Serotype 19A

BY MARY ANN MOON

FROM JAMA

VITALS

**Major Finding:** Sixteen percent of those in the 2 + 1-dose group tested positive for new serotype 19A acquisition, which was significantly higher than the 9% rate in the control group; 13% of children in the 2-dose group did so, but this was not significantly higher than in the control group.

**Data Source:** A post hoc analysis of data from a randomized controlled trial of vaccination in 948 children in the western Netherlands.

**Disclosures:** This study was supported by the Dutch Ministry of Health. Dr. van Gils' associates reported ties to GlaxoSmithKline, Wyeth/Pfizer, Baxter, and Novartis.

Introducing the heptavalent pneumococcal conjugate vaccine into routine infant immunization programs appears to raise the rate of nasopharyngeal acquisition of pneumococcal serotype 19A strains in the first 2 years of life, according to a report.

Researchers had noted a rapid increase in the presence of serotype 19A strains,

which are often multidrug resistant, soon after the widespread implementation of heptavalent pneumococcal conjugate vaccine (PCV7) immunization in several countries. However, they were unsure of a definite link between the vaccine and the emergence of 19A strains because those strains have also increased in some countries without the PCV7 vaccine.

"We now have demonstrated, to our knowledge for the first time, the facilitating role of PCV7 in nasopharyngeal acquisition of serotype 19A. In view of the proven disease potential of serotype 19A for otitis media and invasive pneumococcal disease and its observed association with antibiotic resistance, vaccines of broader coverage including protection against serotype 19A may further aid pneumococcal disease prevention," said Dr. Elske J.M. van Gils of Wilhelmina Children's Hospital, University Medical

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Center Utrecht, the Netherlands, and her associates.

They performed a post hoc analysis of data from a randomized controlled trial in the western Netherlands when PCV7 vaccines were first introduced. The 948 study subjects had been randomly assigned to receive PCV7 at ages 2 and 4 months (the 2-dose group), or PCV7 at ages 2, 4, and 11 months (the 2 + 1-dose group), or no PCV7 (the unvaccinated control group). Nasopharyngeal swabs were then obtained at ages 6 weeks and 6, 12, 18, and 24 months to test for the presence of *S. pneumoniae* and its susceptibility to antibiotics.

The cumulative proportion of children with serotype 19A was significantly higher at the age of 12 and 18 months in both the 2-dose and 2 + 1-dose groups than in the unvaccinated group, but not at 6 months, the investigators said (JAMA 2010;304:1099-106).

Sixteen percent of those in the 2 + 1-dose group tested positive for new serotype 19A acquisition, which was significantly higher than the 9% rate in the control group; 13% of children in the 2-dose group did so, but this was not significantly higher than in the control group. This included the diffuse proliferation of several serotype 19A strains as well as the appearance of new strains.

"Antibiotic resistance or antibiotic consumption could not account for the observed increase," as both resistance and use of antibiotics were extremely low in this population, they noted. One possible explanation is that the reduction in colonization of covered serotypes after vaccination "creates a vacant nasopharyngeal niche where other nonvaccine serotypes, in particular certain 19A clones, may expand."

Bausch & Lomb

**Besivance™**  
besifloxacin ophthalmic  
suspension, 0.6%

**Brief Summary:** Based on full prescribing information revised April 2009.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-323-0000 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### INDICATIONS AND USAGE

Besivance™ (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:

CDC coryneform group G  
*Corynebacterium pseudodiphtheriticum*\*  
*Corynebacterium striatum*\*  
*Haemophilus influenzae*  
*Moraxella lacunata*\*  
*Staphylococcus aureus*  
*Staphylococcus epidermidis*  
*Staphylococcus hominis*\*  
*Staphylococcus lugdunensis*\*  
*Streptococcus mitis* group  
*Streptococcus oralis*  
*Streptococcus pneumoniae*  
*Streptococcus salivarius*\*

\*Efficacy for this organism was studied in fewer than 10 infections.

#### DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once before use.

Instill one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days.

#### CONTRAINDICATIONS

None

#### WARNINGS AND PRECAUTIONS

##### Topical Ophthalmic Use Only

NOT FOR INJECTION INTO THE EYE.

Besivance™ is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

##### Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use of Besivance™ (besifloxacin ophthalmic suspension) 0.6% may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

##### Avoidance of Contact Lenses

Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance™.

#### ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with the rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Besivance™ in approximately 1,000 patients between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.

The most frequently reported ocular adverse event was conjunctival redness, reported in approximately 2% of patients.

Other adverse events reported in patients receiving Besivance™ occurring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

Pregnancy Category C. Oral doses of besifloxacin up to 1000 mg/kg/day were not associated with visceral or skeletal malformations in rat pups in a study of embryo-fetal development, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean C<sub>max</sub> in the rat dams was approximately 20 mcg/mL, >45,000 times the mean plasma concentrations measured in humans. The No Observed Adverse Effect Level (NOAEL) for this embryo-fetal development study was 100 mg/kg/day (C<sub>max</sub>, 5 mcg/mL, >11,000 times the mean plasma concentrations measured in humans).

In a prenatal and postnatal development study in rats, the NOAELs for both fetal and maternal toxicity were also 100 mg/kg/day. At 1000 mg/kg/day, the pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation were delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behavior, including activity, learning and memory, and their reproductive capacity appeared normal.

Since there are no adequate and well-controlled studies in pregnant women, Besivance™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

##### Nursing Mothers

Besifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when Besivance™ is administered to a nursing mother.

##### Pediatric Use

The safety and effectiveness of Besivance™ in infants below one year of age have not been established. The efficacy of Besivance™ in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials [see 14 CLINICAL STUDIES].

There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

##### Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

#### NONCLINICAL TOXICOLOGY

##### Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed.

No *in vitro* mutagenic activity of besifloxacin was observed in an Ames test (up to 3.33 mcg/plate) on bacterial tester strains *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA. However, it was mutagenic in *S. typhimurium* strain TA102 and *E. coli* strain WP2(pKM101). Positive responses in these strains have been observed with other quinolones and are likely related to topoisomerase inhibition.

Besifloxacin induced chromosomal aberrations in CHO cells *in vitro* and it was positive in an *in vivo* mouse micronucleus assay at oral doses  $\geq$  1500 mg/kg. Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rats given the test compound up to 2,000 mg/kg by the oral route. In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 500 mg/kg/day. This is over 10,000 times higher than the recommended total daily human ophthalmic dose.

##### PATIENT COUNSELING INFORMATION

Patients should be advised to avoid contaminating the applicator tip with material from the eye, fingers or other source.

Although Besivance™ is not intended to be administered systemically, quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

Patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Besivance™ or other antibacterial drugs in the future.

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance™.

Patients should be advised to thoroughly wash hands prior to using Besivance™.

Patients should be instructed to invert closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured by: Bausch & Lomb Incorporated  
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U.S. Patent No. 6,685,958

U.S. Patent No. 6,699,492

U.S. Patent No. 5,447,926

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