

# RSV Requires Hospitalizing About 3.4 M Yearly

BY KERRI WACHTER

FROM THE LANCET

An estimated 33.8 million new episodes of respiratory syncytial virus-associated acute lower respiratory infection occurred worldwide in children younger than 5 years of age in 2005, based on results of the first study to take a global view of this deadly infection.

The systematic review and meta-analysis used published and unpublished incidence and mortality data for respiratory syncytial virus (RSV)-associated acute lower respiratory infection (ALRI) in both industrialized and developing countries.

The researchers estimated that worldwide 3.4 million young children developed RSV-associated severe ALRI necessitating hospital admission, and an estimated 66,000-199,000 children

younger than 5 years of age died of the infection. A total of 99% of these deaths occurred in developing countries, reported Dr. Harish Nair and his coauthors (Lancet 2010;375:1545-55).

The authors pointed out that "substantial uncertainty" surrounds case-fatality ratio estimates from developing countries. To that end, the researchers calculated three estimates of RSV-associated ALRI fatalities to assess the upper

and lower bounds, yielding the 66,000-199,000 range.

The incidence of RSV-associated ALRI in developing nations was twice that for industrialized nations. "This estimate represents roughly 22% of all episodes of ALRI in young children," wrote Dr. Nair, who is a public health sciences doctoral student at the University of Edinburgh, and colleagues.

In an accompanying commentary, Dr. Caroline Breese Hall, professor of pediatrics and infectious diseases at the University of Rochester (N.Y.), highlighted the importance of the study.

The researchers "provide the best current estimates of the global under-5 burden of RSV-associated acute lower respiratory tract infections, and convincingly

**VITALS** **Major Finding:** Mortality related to RSV infection worldwide was estimated to be 66,000-199,000 in children younger than 5 years in 2005, with a total of 99% of these deaths occurring in developing countries.

**Data Source:** Systematic review of 36 incidence studies, including 10 unpublished studies.

**Disclosures:** Study funded by the World Health Organization and the Bill & Melinda Gates Foundation.

posit the virus as the foremost cause of all lower respiratory tract infections in young children worldwide," she said (Lancet 2010;375:1500-2).

The researchers started by performing a systematic literature review using a combination of search terms, manual searching of online journals, and scanning reference lists of identified citations. Studies were limited to those from January 1995 to June 2009. In addition, the researchers "invited the participation of researchers who had done similar studies resulting in unpublished data or supplementary data from published work."

As inclusion criteria, the researchers chose to use ALRI and severe ALRI, including bronchiolitis and pneumonia. ALRI was considered the presence of cough or difficulty breathing with indrawing of the lower chest wall with fast breathing for age. Severe ALRI was considered the presence of cough or difficulty breathing with indrawing of the lower chest wall (with or without fast breathing for age) that required hospitalization.

They identified 36 studies with suitable data: 19 published population-based studies, 7 published studies based on hospital discharge records and laboratory diagnosis reports, and 10 unpublished population-based studies. The researchers noted that few studies reported data for the full age range (0-5 years).

The researchers performed a meta-analysis of incidence data and reported pooled estimates using the random effects model. They estimated the incidence for industrial and developing countries for 2005 and summed these estimates to get a global incidence estimate. ■



**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 ≥ 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  
 Tampa, Florida 33637  
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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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