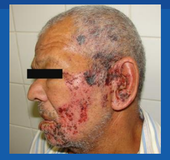

# Family History as a Risk Factor for Herpes Zoster: is Herpes Zoster Risk Heritable?


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## BACKGROUND

- Almost 1 in 3 persons experience herpes zoster (HZ) during their lives, translating to ~1 million episodes annually in the U.S.; episodes can cause disabling and prolonged pain and other complications
- HZ is caused by reactivation of latent varicella zoster virus (VZV)
  - Both wild-type VZV (WT-VZV) and vaccine-strain VZV (VS-VZV) can reactivate, although the risk from VS-VZV appears to be much lower than that from WT-VZV[1,2]
  - Virtually all persons are latently infected with either WT-VZV (i.e., recalled or unrecalled history of varicella) or VS-VZV (i.e., history of varicella vaccination), or both[3,4]
- Risk factors for HZ are older age and immunosuppression, but these factors generally do not explain why some persons develop HZ and others do not
- Knowledge of HZ risk factors would provide clues for mechanisms underlying VZV reactivation, help explain the epidemiology of HZ, and could lead to better strategies for prevention
- Genetic predisposition is a potential risk factor for many illnesses. Several studies suggest HZ is heritable; all relied on self-report and were subject to recall and other bias[5-10]

## STUDY OBJECTIVE

- We used data from a large national administrative database to assess whether medically-attended HZ is associated with HZ in family members
  - WT- and VS-VZV differ in many ways: age at "infection," size & route of inoculum, risk of reactivation, potential for misclassification, impact on HZ risk in contacts (via exogenous boosting); biologically, VZV strain may interact differently with heritability too. We therefore evaluated the associations by WT-VZV and VS-VZV strata as well.

## METHODS

- **Data Source:**
  - Claims data from Truven Health MarketScan® Databases, 1998-2014
  - Beneficiary and co-beneficiary data for millions of enrollees from public and private employers and health insurance plans
- **Study Population:**
  - MarketScan enrollees
    - Sibling analysis: having ≥2 children in which oldest 2 are concordant for either WT-VZV or VS-VZV infection (definitions below)
    - Parent analysis: having ≥1 children (definition below)
    - Spouse analysis: having 1 spouse or if >1 spouse, the oldest spouse (definition below) and ≥1 children
- **Study Definitions:**
  - Family: primary beneficiary with his or her co-beneficiaries
    - Child: a co-beneficiary with documented births (based on ICD-9 codes) between 1998 – 2014 (i.e., maximum age of 16 years)
      - Index: the oldest child in the family
      - Sibling: the second oldest child in the family
    - Parent: a primary beneficiary of ages 18 - 64
    - Spouse: the co-beneficiary of ages 18 - 64
  - HZ: defined using ICD-9 codes (053.XX) occurring between 1998-2014
  - VS-VZV infected: defined using CPT codes for varicella vaccination (90716, 90710) during 1998-2014
  - WT-VZV infected: defined by ABSENCE of CPT codes for varicella vaccination during 1998-2014
  - Family history of HZ: occurrence of HZ in the index child during 1998-2014
- **Data Analysis**
  - Sibling analysis: HZ risk in sibling in families with vs. without family history of HZ
  - Parent analysis: HZ risk in parent in families with vs. without family history of HZ
  - Spouse analysis: HZ risk in spouse in families having parent with vs. without history of HZ
  - VZV strain analysis: impact of family history on HZ risk when children are infected with VS-VZV vs. WT-VZV
  - Relative risks (RR) with corresponding 95% confidence interval and p-values were calculated.

## RESULTS

**TABLE 1: Risk of HZ in siblings or parents when index child did or did not experience HZ***

| | Index child HZ positive | Index child HZ negative | Relative Risk |
|---|---|---|---|
| | n | n | (95% CI, p-value) |
| Children WT-VZV infected | | | |
| Sibling (N=59,920) | 76 | 59,844 | 28.5 (4.1, 198.0, p = 0.03) |
| Parent (N=1,457,046) | 13,176 | 1,443,870 | 6.3 (4.5, 8.7, p < .0001) |
| Children VS-VZV infected | | | |
| Sibling (N=181,579) | 323 | 181,256 | 12.6 (4.8, 33.5, p < .0001) |
| Parent (N=1,297,324) | 24,298 | 1,273,026 | 2.1 (1.6, 2.7, p < .0001) |
| Children regardless of VZV | | | |
| Sibling (N=241,499) | 399 | 241,100 | 14.7 (6.2, 35.2, p < .0001) |
| Parent (N=2,754,370) | 37,474 | 2,716,896 | 3.3 (2.6, 4.0, p < .0001) |

**TABLE 2: Risk of HZ in spouses when parent child did or did not experience HZ (non-heritable controls)***

| | Index child HZ positive | Index child HZ negative | Relative Risk |
|---|---|---|---|
| | n | n | (95% CI, p-value) |
| Spouses of parents | | | |
| Index child WT-VZV (N=1,032,871) | 8,059 | 1,024,812 | 3.2 (2.8, 3.7, p < .0001) |
| Index child VS-VZV (N=1,011,085) | 17,882 | 993,203 | 1.9 (1.8, 2.1, p < .0001) |
| Index child, all (N=2,043,956) | 25,941 | 2,018,015 | 2.5 (2.3, 2.6, p <.0001) |

* Abbreviations: HZ, herpes zoster; WT-VZV, wild-type varicella zoster virus; VS-VZV varicella vaccine-strain

- Siblings of HZ positive index children had 14.7 times the rate of HZ compared to those with HZ negative index children (Table 1)
- Parents of HZ positive index children had 3.3 times the rate of HZ compared to parents of HZ negative index children (Table 1)
- VZV strain influences the results: in the sibling analysis, the differences were not significant (p = 0.46) but in parent analysis they were (p < .0001)
- Spouses of HZ positive parents were at greater risk of HZ compared to spouses of HZ negative parents (when either VS- or WT-VZV infected index children) showing that our analysis may be influenced by non-heritable factors (Table 2)
- We looked among WT- and VZ-VZV strata at calendar years of observation time and age of parents to see if differences were large and could be causing important bias
  - In sibling analysis, the median year of when observation time began (birth of index child) was 2009 vs. 2007 for WT- and VS-VZV strata, respectively, and in parent analysis the median years were 2010 and 2009, respectively (i.e., observation time similar across strata for these analyses)
  - The median age of parents was 31 and 32 years of age for WT- and VS-VZV strata, respectively (i.e., median age similar for these analyses)

## LIMITATIONS

- Misclassification:
  - Family (child/sibling/parent/spouse) defined via co-beneficiary status
  - HZ (for establishing risk [family history] or outcome [HZ]):
    - HZ diagnosis is fairly specific, even for children*
    - HZ diagnosis is likely insensitive in children: it's mild (parents may ignore it; doctors may misdiagnose it). It's likely even less sensitive when due to VS-VZV: milder than HZ due to WT-VZV
  - VZV strain: varicella (WT-VZV) defined as lack of vaccination (~90% of varicella is not captured by Marketscan, vaccination is rarely missed). This could lead to misclassification:
    - VS-VZV as WT-VZV (if vaccine costs aren't charged for some reason
    - VZV-negative children (neither varicella nor vaccine) as WT-VZV
  - Many of these sources of error would lead to conservative bias
- Differences in HZ risk within families may also be influenced by:
  - Shared non-heritable risk factors (environmental or behavioral)
  - VZV-strain: low HZ risk in VS-VZV positive siblings would increase attributable role of heredity (i.e., RR)
  - Shared healthcare access or health seeking behavior for HZ
  - Exogenous boosting by varicella exposure may reduce HZ risk yet only occur for WT-VZV, not VZ-VZV
- On occasion HZ in parent or sibling would cause WT-VZV in a child

## CONCLUSIONS

- Our analyses suggest that HZ risk is heritable
- Our methods clearly have limitations, however:
  - Many of misclassification errors would be conservative
  - We used controls to look for non-heritable effects; associations were seen but of lower magnitude suggesting (certainly not proving) that some of our observed associations are real
  - Given the factors noted above, our estimates are quite variable; we cannot use our results to derive a single estimate of association
- Heritability of HZ risk has important scientific and practical implications
- Our methods are based on medically-attended data
  - They complement recall-based studies, which are prone to bias
  - These methods provide an alternative approach to studying heritability for a wide variety of medical conditions

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