The association between vaccine coverage and herd protection: exploratory analyses of a cluster-randomised trial of Vi conjugate vaccine

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Background

- Two typhoid vaccines studied by CRCT:
  - Vi polysaccharide vaccine, made from the purified Vi capsular polysaccharide from the Ty2 Salmonella Typhi strain
  - Vi-tetanus toxoid conjugate vaccine (TCV), using tetanus toxoid as the carrier protein with Vi polysaccharide

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vi polysaccharide vaccine</th>
<th>Vi-tetanus toxoid conjugate vaccine (TCV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine efficacy</td>
<td>61% in Kolkata$^1$</td>
<td>85% in Bangladesh$^2$</td>
</tr>
<tr>
<td>Indirect protection</td>
<td>Significant indirect protection (45%)</td>
<td>No evidence</td>
</tr>
<tr>
<td>Vaccine population</td>
<td>Residents aged &gt;24 mths</td>
<td>Children aged 9 mths - &lt;16 yrs</td>
</tr>
<tr>
<td>Vaccine coverage</td>
<td>61%</td>
<td>20%</td>
</tr>
</tbody>
</table>

- **Question:** Does the vaccine coverage have an impact on the herd protection?

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Description of TyVAC Bangladesh

- Cluster randomised controlled trial of TCV efficacy in children (9 mths to <16 yrs)
- Apr 15, 2018 - March 15, 2020
- 150 contiguous clusters, 1:1 to either TCV or SA 14-14-2 Japanese encephalitis (JE) vaccine
- 67,395 children vaccinated (33,727 TCV and 33,315 JE)
- Baseline census between Feb 14, and March 25, 2018 (updated semiannually)
- Surveillance for typhoid fever started in Feb 2018 (all population)
- Patients with ≥2 days fever or axillary temperature of ≥ 38C taken blood culture
Cluster Randomised Controlled Trial

vs. protection for vaccinated persons

vs. protection for unvaccinated persons
Methods

• Cluster-level
  ➢ Question: whether the herd protection increases with the increase in cluster-level vaccine coverage
  ➢ 75 TCV (JE) clusters, 4 groups, based on the quantile of vaccine coverage rate (17% - 26%)

• Family-level:
  ➢ Question: whether the herd protection on adults of a family increases with the increase in the number of vaccinated children in the family
  ➢ Families in TCV (JE) arm, 4 groups, based on the number of TCV (JE) recipients

• School-level:
  ➢ Question: whether the herd protection on non-TCV vaccinated children (JE + non-vaccinees) increases with the increase in the school-level TCV coverage
  ➢ School information collected by additional questionnaire
  ➢ 35 schools with a size of >100 students, 2 groups, based on TCV coverage rate* (8% - 55%)
Methods: Cluster-level

TCV clusters in group 1 (Q1)
17%-19%

TCV clusters in group 2 (Q2)
19%-20%

TCV clusters in group 3 (Q3)
20%-22%

TCV clusters in group 4 (Q4)
22%-26%

JE clusters in group 1 (Q1)
17%-19%

JE clusters in group 2 (Q2)
19%-20%

JE clusters in group 3 (Q3)
20%-21%

JE clusters in group 4 (Q4)
21%-25%

TCV clusters vs. JE clusters

Received TCV

Received JE

Non-vaccinees (child, adult)

IRR in Q1

IRR in Q2

IRR in Q3

IRR in Q4
## Results: Cluster-Level

<table>
<thead>
<tr>
<th></th>
<th>N/PYs</th>
<th>Incidence, per 100,000 PYs</th>
<th>Adjusted VE [%]</th>
<th>P value for interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JE</td>
<td>TCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>71/9,664</td>
<td>12/9,702</td>
<td>735</td>
<td>124</td>
</tr>
<tr>
<td>Q2</td>
<td>68/10,309</td>
<td>13/10,207</td>
<td>660</td>
<td>127</td>
</tr>
<tr>
<td>Q3</td>
<td>68/10,217</td>
<td>10/9,938</td>
<td>666</td>
<td>101</td>
</tr>
<tr>
<td>Q4</td>
<td>47/11,550</td>
<td>9/12,062</td>
<td>407</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>23/5,423</td>
<td>19/5,483</td>
<td>424</td>
<td>347</td>
</tr>
<tr>
<td>Q2</td>
<td>23/5,079</td>
<td>20/5,048</td>
<td>453</td>
<td>396</td>
</tr>
<tr>
<td>Q3</td>
<td>20/4,618</td>
<td>29/4,416</td>
<td>433</td>
<td>657</td>
</tr>
<tr>
<td>Q4</td>
<td>13/4,985</td>
<td>12/4,921</td>
<td>261</td>
<td>244</td>
</tr>
<tr>
<td>Q1</td>
<td>47/44,338</td>
<td>49/43,780</td>
<td>106</td>
<td>112</td>
</tr>
<tr>
<td>Q2</td>
<td>47/42,592</td>
<td>39/42,589</td>
<td>110</td>
<td>92</td>
</tr>
<tr>
<td>Q3</td>
<td>44/39,308</td>
<td>41/38,464</td>
<td>112</td>
<td>107</td>
</tr>
<tr>
<td>Q4</td>
<td>43/40,433</td>
<td>25/40,129</td>
<td>106</td>
<td>62</td>
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N/PYs: Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up
Adjusted IRR: Adjusted Incidence Rate Ratio, using Poisson regression adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility), covariates (age, gender, household toilet type, household source of drinking water, household type of drinking water, hand wash before meal, and hand wash after defecation), and random effect (cluster).

* Interaction between quantile group and arm
Methods

- Cluster-level
  - Question: whether the herd protection increases with the increase in cluster-level vaccine coverage
  - 75 TCV (JE) clusters, 4 groups, based on the quantile of vaccine coverage rate (54% - 72%)

- Family-level:
  - Question: whether the herd protection on adults of a family increases with the increase in the number of vaccinated children in the family
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- School-level:
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  - School information collected by additional questionnaire
  - 35 schools with a size of >100 students, 2 groups, based on TCV coverage rate* (8% - 55%)
Methods: Family-level

[Diagram showing family-level clusters with TCV and JE vaccine status]
Results: Family-level

IRR in adults of families with no vaccinated children (with age-eligible children)

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<tr>
<th>Number of vaccinated children</th>
<th>N/PYs (n)</th>
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<td>0</td>
<td>11/26,408 (n=23,206)</td>
<td>10/25,409 (n=22,740)</td>
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<td>39</td>
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N/PYs(n): Blood-culture confirmed typhoid fever (no.)/ Person-Years of follow-up (number of adults >18 yrs)

Adjusted IRR: Adjusted Incidence Rate Ratio, using Poisson regression adjusted for design variables (the number of children 9 months to <16 years of age, ward and distance of cluster to the nearest health facility), covariates (age, gender, household toilet type, household source of drinking water, household type of drinking water, hand wash before meal, and hand wash after defecation ), random effect (cluster), and number of eligible children for vaccination

* Interaction between family group and arm
Outcome: Family-level

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<td>1</td>
<td>27/35,069 (n=30,015)</td>
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</tr>
<tr>
<td>2 &amp; 3</td>
<td>10/29,206 (n=24,154)</td>
<td>10/29,105 (n=24,574)</td>
<td>34 (n=24,154)</td>
<td>34 (n=24,574)</td>
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Methods: School-level

Incidence of typhoid compared between non-TCV recipients in high TCV coverage schools and that in low TCV coverage schools
Results: School-Level

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<tr>
<td><strong>Non-TCV recipients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>10/4,785 (n=3,101)</td>
<td>209</td>
<td>Ref</td>
</tr>
<tr>
<td>Above median</td>
<td>11/3,269 (n=2,178)</td>
<td>337</td>
<td>-7 [-4268,97]</td>
</tr>
<tr>
<td><strong>TCV recipients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>1/2,018 (n=1,217)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Above median</td>
<td>1/2,468 (n=1,445)</td>
<td>41</td>
<td></td>
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Summary

• Our study did not find an association between vaccine coverage and herd protection

• Vaccinating children may not result in a detectable level of herd protection in Bangladesh
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Major Contributors

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- PATH
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- icddr,b
- OuCru
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Learn more at:
http://takeontyphoid.org