Electronic Supplementary Material # 1:

Benefit-risk monitoring of vaccines using an interactive dashboard: a methodological proposal from the ADVANCE project

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Interactive dashboard for benefit-risk monitoring

The architecture of the dashboard contains the following distinct steps (Figure S.1):

- Pre-processing 1: This step starts from the electronic healthcare data and transforms it into an individual level analytical dataset containing the exposure, outcome and covariate information of interest. For developmental purposes, we simulated the analytical dataset.
- Pre-processing 2: This step starts from the individual-level analytical data and transforms it into various data tables containing aggregated data needed to produce the charts displayed by the web-application. The data tables contain aggregated data such as weekly number of active patients and events by age groups, weekly number of active subjects by age group and person time information.
- Web application: The web-application is an interactive dashboard allowing end-users to visually explore benefit-risk measures and their components. The inputs of the chart generating functions are the data tables generated in the second pre-processing step as well as some user-defined settings (e.g. age groups, baseline incidences and preference weights).

The web application can be accessed using the following public URL: http://apps.p-95.com/BRMonitor/. The major advantage of using a web interface is its user-friendliness in accessibility and usage; the end-user can use a web browser of choice to access the dashboard without the need to install or understand R and the underlying electronic healthcare data can be

seamlessly updated. The architecture allows for secure storage of the individual-level data as the web-application only uses as input the aggregated data generated by the second pre-processing step. The pre-processing steps, which use the individual-level data, only need to be performed when the healthcare data is updated and can be done separately using a dedicated, secured server.

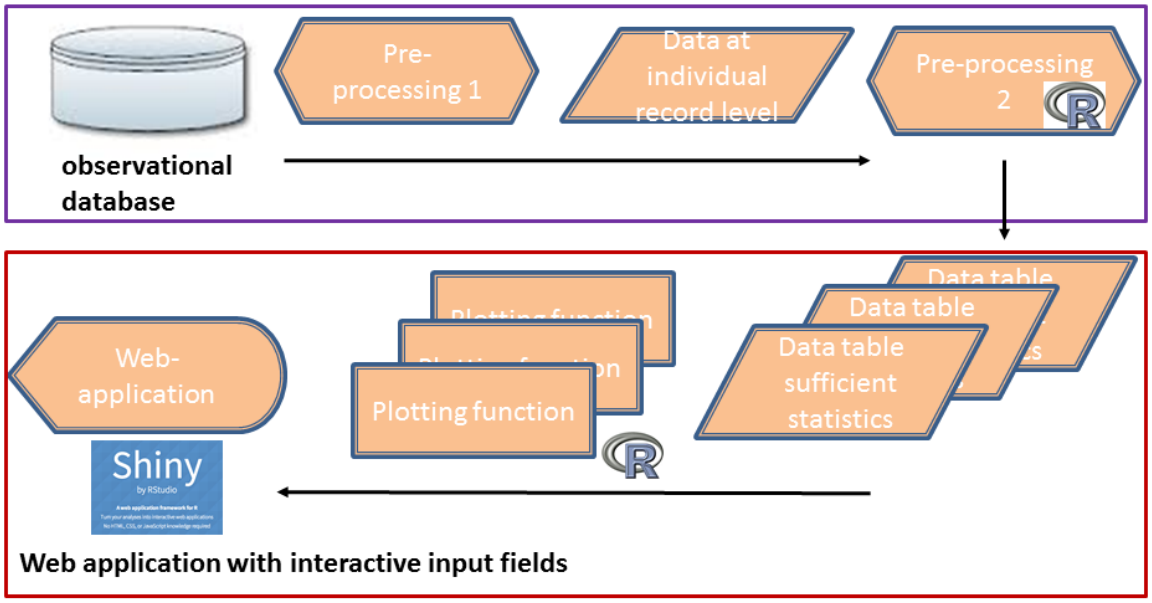

Figure S.1: Architecture of the interactive dashboard for benefit-risk monitoring of vaccines.

Electronic Supplementary Material # 2:

Benefit-risk monitoring of vaccines using an interactive dashboard: a methodological proposal from the ADVANCE project

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Detailed description of the visualizations for monitoring

S2.1. Coverage

Weekly doses extrapolated to the whole UK population

Let n_{ij} denote the total number of doses given during week i by age group j as estimated from the database. Then, the total number of doses extrapolated to the whole UK population is calculated as

$$Ntot_{ij} = (N_{ij}/pop_j)^{-1} n_{ij} = w_{ij}\, n_{ij}, \quad (1)$$

where N_{ij} is the number of active subjects within the database by week i and age group j en where pop_j is the number of subjects in the total UK population of age group j obtained from the National Office of Statistics, UK. As such, the weights w_{ij} can be interpreted as inverse sampling weights.

Coverage

Let n_{ij} denote the total number of vaccinated children at week i of age group j and let N_{ij} denote the total number of children. Then, coverage p at week i for age group j is simply obtained as

$$p_{ij} = n_{ij}/N_{ij} \quad (2)$$

S2.2 Risks

Intussusception incidence rates; baseline incidences and within risk windows

The person-time incidence rate (per 10,000 person years) of intussusception by week I is estimated cumulatively over time, using all data accrued from the start of the study period/vaccination period till week I or

$$inc_I = \left(\sum_{i=1}^{I} n_i \Big/ \sum_{i=1}^{I} py_i \right) \times 10{,}000, \quad (3)$$

where n_i is the number intussusception events that happened during week i and where $py_i$is the amount of person time (in years) within that week.

The baseline incidence rates of intussusception are estimated using data from the start of the study period till the start of the vaccination period. The incidence rates of intussusception following immunization during two consecutive risk windows (1-7 and 8-21 days post-vaccination) after dose 1 and dose 2 are estimated using data from the start of the vaccination period till the end of the study period.

S2.3 Benefits

The person-time incidence rate (per 10,000 person years) of RVGE GP visits and of hospital admissions by week I is estimated using data within a 'window' of width Δ, covering data from week I and looking backwards till week $I - \Delta$, or

$$inc_I = \left(\sum_{i=I-\Delta}^{I} n_i \Big/ \sum_{i=I-\Delta}^{I} py_i \right) \times 10{,}000, \quad (4)$$

where n_i is the number events that happened during week i and where $py_i$is the amount of person time (in years) within that week.

For comparison, we also predicted the expected incidence rates of RVGE GP visits and of hospital admissions given assumed levels of vaccine effectiveness and age-specific baseline incidence accounting for the vaccination coverage and age structure within the healthcare database. Particularly, we calculated the expected weekly number of cases as

$$E(n_i) = \sum_{j=1}^{J} py_{ij} \times \frac{E_{0j}}{10{,}000} \times \Big(p_{ij}(1 - VE) + \big(1 - p_{ij}\big)\Big), \qquad (5)$$

where py_{ij} is the age- and week-specific person time (in years), $p_{ij}$is the age- and week-specific coverage and where E_{0j} refers to the assumed age-specific baseline incidences and VE to the assumed vaccine effectiveness. Then, the expected incidence is calculated similarly as in (4) but using the expected counts instead or,

$$E(inc_I) = \left(\sum_{i=I-\Delta}^{I} E(n_i) \Big/ \sum_{i=I-\Delta}^{I} py_i\right) \times 10{,}000. \qquad (6)$$

S2.4 Benefit-risk

Benefit-risk measures

The INHB is defined as

$$\Delta'_i = \sum_{k=1}^{K} w_k \times (E_{0k} - E_{vki}) + \sum_{k=1}^{K'} w_k \times (R_{0k} - R_{vki}) = \boldsymbol{E_i} + \boldsymbol{R_i}. \qquad (7)$$

where K and K' refer to the number of benefit and risk outcomes, where the incremental benefits are the difference between the benefits in the absence of vaccination or baseline benefits ($E_{0.}$) and the benefits after vaccination ($E_{v.}$), and similarly for the incremental risks ($R_{0.}$ and $R_{v.}$). The weights w_k are all positive and reflect the relative severity of the health outcomes. Note that, because $E_{v.}$and $R_{v.}$ are subtracted from their baseline values, the incremental benefits ($\boldsymbol{E}$) are positive and the incremental risks ($\boldsymbol{R}$) negative.

For the example of B/R of rotavirus vaccination, we derived the incremental benefits by taking the difference between the incidence (/10,000) of RVGE GP visits and hospital admissions before and after vaccination. The incremental intussusception risk was derived from the attributable risk, which was subsequently multiplied with the total number of intussusception cases within the risk windows to obtain the attributable number of cases, which were then used to calculate the attributable incidence (/10,000).

Then, making the Poisson approximation to the binomial variance of the incidences (Armitage & Berry, 1987), the variance of the INHB is

$$\sigma^2(\Delta'_i) = \sum_{k=1}^{2} (w_k)^2 \left(E_{v\,k\,i} \times {}^{10{,}000}/_{py_{v\,ki}}\right) + \sum_{k=1}^{1} (w_k)^2 \left(R_{attr\,ki} \times {}^{10{,}000}/_{py_{v\,ki}}\right)$$

$$= \sigma^2(\boldsymbol{E_i}) + \sigma^2(\boldsymbol{R_i}) \qquad (8),$$

with weights w_k and post-vaccination person time $py_{v\,.}$ and where $E_{v.}$ is the incidence (per 10,000) of the RVGE GP visits and hospitalization outcomes post-vaccination and where $R_{attr.}$ is the attributable intussusception incidence. The baseline incidences $E_{0\,k}$ in (7) are assumed to be known. The 95% Wald confidence intervals are then obtained as $CI = \Delta'_i \pm 1.96 \times \sqrt{\sigma^2(\Delta'_i)}$.

The IBRR uses the same terms $\boldsymbol{E_i}$ and $\boldsymbol{R_i}$ as in (7), but uses the ratio instead, or

$$\Omega'_i = {}^{\boldsymbol{E_i}}/_{-\boldsymbol{R_i}}. \qquad (9)$$

The variance is then expressed as

$$\sigma^2(\ln(\Omega_i')) = {}^{\sigma^2(\boldsymbol{E_i})}\Big/_{\boldsymbol{E_i}^2} + {}^{\sigma^2(\boldsymbol{R_i})}\Big/_{\boldsymbol{R_i}^2}, \qquad (10)$$

with the 95% Wald confidence intervals equal to $CI = e^{\ln(\Omega'_i) \pm 1.96\sqrt{\sigma^2(\ln(\Omega'_i))}}$. In case of theoretical benefits, $\sigma^2(\boldsymbol{E_i}) = 0$.

References:

Armitage P, Berry G. Statistical methods in medical research. 1987, Oxford: Blackwell Scientific.