How did the adoption of wP-pentavalent affect the global paediatric vaccine coverage rate? A multicountry panel data analysis

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ABSTRACT

Objectives Several studies have highlighted the effects of combination vaccines on immunisation coverage at the national or subnational level. This study examined the effects globally. Worldwide introduction of whole-cell pertussis pentavalent (wP-pentavalent) allowed estimation of incremental coverage effects of combination vaccines on the third doses of diphtheria, tetanus, pertussis (DTP3); hepatitis B (HepB3) and Haemophilus influenzae type B (Hib3).

Methods Multicountry panel data analysis.

Data sources Country-level vaccine coverage data of WHO/UNICEF for the years 1980–2018.

Methods Linear mixed models were used to estimate the effects of wP-pentavalent introduction by incorporating proxy variables to control for time trend and other time-dependent changes in the immunisation programmes.

Results Introduction of combination vaccines may have improved the coverage of DTP3 by percentage points (95% CI 2.5% to 3.6%) globally compared with the coverage in the precombination vaccine era. The comparison of coverage rates of HepB3 and Hib3 in before and after wP-pentavalent periods indicates that the introduction of combination vaccines improved the coverage by 10.1 percentage points (95% CI 8.4% to 11.7%) for HepB3 and 9.9 (95% CI 7.1% to 12.7%) for Hib3 in countries that introduced those antigens prior to adoption of wP-pentavalent. Even though the incremental coverage increase of DTP3 appears quite modest, it is still a significant result, especially because DTP vaccine coverage (90%) worldwide against these diseases by 1990. The programme was successful in lowering the under-5 mortality from 17 million in 1970 to 12.8 million in 1990 and to 10.5 million in 2000. Despite initial significant improvements, about 3 million children died from pneumococcal diseases, measles, hepatitis B (HepB) and Haemophilus influenzae type B (Hib) infections in 1999–2000. Effective vaccines were available to prevent these deaths but most children in the low and lower middle-income countries did not have access to the vaccines due to several factors, including the fact that they were not included in the National Immunization Programmes by 2018.

Conclusion The findings suggest that development of combination vaccines with additional antigens is likely to help sustain and improve coverage of existing as well as new childhood vaccines.

INTRODUCTION

The adoption of Expanded Program on Immunization (EPI) in 1974 by the WHO was instrumental in improving the coverage of vaccines against six preventable diseases (tuberculosis, poliomyelitis, diphtheria, tetanus, pertussis and measles). The initial WHO’s target was to achieve high rates of vaccine coverage (90%) worldwide against these diseases by 1990. The programme was successful in lowering the under-5 mortality from 17 million in 1970 to 12.8 million in 1990 and to 10.5 million in 2000. Despite initial significant improvements, about 3 million children died from pneumococcal diseases, measles, hepatitis B (HepB) and Haemophilus influenzae type B (Hib) infections in 1999–2000. Effective vaccines were available to prevent these deaths but most children in the low and lower middle-income countries did not have access to the vaccines due to several factors, including the fact that they were not included in the National Immunization Programmes by 2018.
Immunization Program (NIP). By 2000, less than 10% of low-income countries had adopted HepB vaccination and less than 5% had introduced Hib vaccine. This situation improved significantly after the creation of Gavi, the vaccine alliance in 2000. Gavi provided financial support, health systems and immunisation activities strengthening, technical country assistance among others to low-income countries for the adoption of new antigens in their immunisation schedule including HepB and Hib. Introduction of whole-cell pertussis (wP)-pentavalent vaccines not only allowed the simultaneous delivery of two new antigens such as HepB and Hib, but also reduced the number of shots from nine to three compared with the shots needed when all the vaccines, that is, the vaccines against diphtheria, tetanus, wP (DTwP vaccine ×3), HepB (×3) and Hib (×3) were to be delivered separately. Therefore, the introduction of pentavalent (DTwP–Hib–HepB) vaccines is considered to have helped the increase in coverage with either no increase or reductions in the number of shots, easing the introduction of vaccines against other diseases. In 2020, the 20th anniversary of Gavi’s support for pentavalent introduction, 73 low-income countries of the world had adopted pentavalent vaccines in their routine immunisation programmes. From 2001 to 2020, introduction of pentavalent vaccines (DTwP–Hib–HepB) is estimated to have averted 10 million deaths and 390 million disability-adjusted life years, generating a total economic benefit of $250 billion from only the Hib and HepB components of these pentavalent vaccines. During this period, Gavi’s total disbursements on pentavalent vaccines procurement were less than $4.0 billion, implying high economic return on investment.

Several studies have highlighted the benefits of combination vaccines in improving vaccine coverage rates. A national cohort study conducted in Australia in 2013–2014 found that a combined measles–mumps–rubella–varicella (MMRV) vaccine improved coverage of measles vaccination by 4% and on-time immunisation with the second MMR dose increasing from 59% to 72%. Two other studies reported significant improvements in varicella vaccine coverage with the adoption of MMRV. Comparison of two groups of children in the USA, one group receiving combination vaccines DT acellular pertussis (DTaP)–inactivated poliovirus vaccine (IPV)–HepB and the other group receiving the vaccines separately, found that vaccination completion was higher in the ‘combination vaccines’ group. The combination vaccines group was also more likely to receive the vaccines in a timely manner. In general, combination vaccines help parents and providers to overcome the complexity of vaccination schedules, increasing coverage and improving the timeliness of vaccination.

A literature review by Maman et al identified a number of benefits of adopting combination vaccines and the benefits obtained were categorised into two groups: societal value and public health/economic value. The societal values of combination vaccines were improved compliance and timeliness of vaccination, better protection against childhood diseases, lower likelihood of pain and suffering, and fewer potential local injection site side effects due to reduced number of injections, better acceptance of combination vaccines from parents, willingness to pay additional money by parents to avoid extra injections, reduced opportunity cost of time for parents and caregivers as the number of visits needed to healthcare providers declines to receive childhood vaccines, improved efficiency of healthcare providers due to lower time input needed to administer one injection rather than multiple injections, improved safety of healthcare providers with the reduction in the risk of needle-stick injury. Another systematic review found a host of psychological predictors associated with not vaccinating a child. Although combination vaccines were not the focus of the review, a number of concerns and barriers to improve immunisation identified were clearly related to the number of injections received by children during immunisation visits. For example, few specific reasons cited as discouraging childhood immunisation were ‘injections are traumatic’, ‘logistic barrier or inconvenient time’, ‘need for receiving multiple doses’, etc. A relatively small study reported that 37% of children deferred some of the vaccine doses during a visit and the deferment was strongly associated with the number of vaccine injections due at the visit.

By 2018, about 86% of children of the world were fully immunised against diphtheria, tetanus and pertussis (DTP) defined by the coverage of the third dose of DTP (DTP3). Coverage of all childhood vaccines has consistently improved over the years since 1980 but the improvements have slowed significantly since 2010. For example, coverage of DTP3 increased just 2% from 2000 to 2018 (84% to 86%), resulting in more than 94 million under-5 children still undervaccinated or unvaccinated in the year 2018, that is, without accounting for late doses which are not routinely measured. Moreover, geographical difference in childhood immunisation coverage varied from about 76% in Africa to more than 90% in the European region. Many countries in the European, North American and Latin American, Asia-Pacific and Middle East regions use aP combination vaccines rather than the wP-containing combination vaccines and it is known that use of acellular-type combination vaccines explains a part of the coverage gap between those countries and the low and lower middle-income countries. In any case, adoption of combination vaccines is considered one of the potential approaches for improving vaccine coverage rates to reach the WHO target of 90%.

To ensure continued success of childhood vaccination and further improvements in child survival, in all countries, especially the low and middle low income, vaccination coverage rates will have to improve. Even though significant progress has been achieved, further improvements will require addressing the underlying causes of vaccine hesitancy. With the recommendation from WHO in 2014 of at least one dose of IPV in the immunisation schedule, an additional injection has been added. The
upcoming licensure of currently under development wP-IPV hexavalent (DTwP–HepB–Hib–IPV) vaccines, and their potential introductions in NIPs, may help increase IPV coverage where it is low and sustain it where it is high. Given that wP-pentavalent vaccines began to be introduced in different countries of the world since 2000, analysis of the effects of introduction of pentavalent on completion of the third DTP primary dose (DTP3) will provide important information about the value of more complete combination vaccines to expand vaccine coverage rates.

Thus, the objective of the paper is to examine the effect of introducing whole-cell pentavalent vaccine on the coverage of DTP3, third doses of Hib (Hib3) and HepB (HepB3). Rather than looking at one country or one region, the perspective of the analysis is all countries where wP-pentavalent vaccines are being used in their NIPs. Since the adoption of wP-pentavalent vaccines has become generalised and widespread due to the support low-income and lower middle-income countries have received from Gavi, it should be possible to quantify the effect of wP-pentavalent vaccine adoption on the coverage rates of different childhood vaccines at the global level. To our knowledge, this is the first study that has been conducted with an analysis at the global level.

METHODS
Conceptual model of vaccine uptake
The demand for childhood vaccines should depend on the perceived costs and benefits of vaccinations from the perspective of parents/caregivers. Parents, in theory, decide to accept or not accept an additional antigen in the immunisation schedule by comparing the benefits (B) and the costs (C) associated with the antigen. For the i-th antigen, if \( B_i > C_i \), the i-th antigen will be accepted. Additional antigen prevents additional childhood diseases and therefore, the perceived benefits should be higher. Perceived cost can also increase if the new antigen creates significant adverse effects and/or requires additional injections. Marginal cost of additional injection may also be higher with increasing number of shots. If the added antigen does not require additional shot or if the number of shots actually goes down with the introduction of new antigens, perceived costs should not increase but perceived benefits will improve, increasing the demand for vaccines. Increasing demand, however, may not lead to higher uptake of vaccines if supply constraints restrict utilisation. Therefore, concurrent improvements in supply environment and access to vaccines may be needed for translating increased demand into increased coverage.

A study found that 23% parents in the USA considered too many antigens in the vaccine schedule as creating ‘antigenic overload’. This perception is not supported by scientific evidence; in fact, it has clearly been demonstrated that cumulative vaccine antigen exposure is associated with higher level of protection against non-vaccine-targeted infections. Even maximum single-day antigen exposure shows no adverse effect on protection against infectious diseases. Therefore, the increasing number of vaccines in the schedule actually increases the benefit of vaccination. Pollard and Bijker present a comprehensive review of studies on these topics.

Data and data sources
Vaccination data of different countries of the world are available through several sources including WHO, UNICEF and country-level immunisation programmes. The WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) is the principal source of information for this analysis. The WUENIC information goes through a few quality checks including the consideration of contextual factors like stock-outs. In case of very few missing information, country-level programme information was accessed to obtain a complete set of vaccine coverage data by antigens for the years 1980–2018. Information on economic status of the countries around 2018 was obtained from the World Development Indicators of the World Bank. Based on the World Bank classification, countries were categorised as either low income, lower middle income, upper middle income and high income.

Introduction of pentavalent vaccines, by definition, adds Hib and HepB in the NIP if the country did not have these vaccines prior to the adoption of the combination vaccines. For these countries, coverage of Hib and HepB will show significant increase with pentavalent introduction simply because these antigens are part of the pentavalent vaccines. As such, inclusion of these countries in the estimation of ‘coverage effect’ of pentavalent vaccines on Hib and HepB will overestimate the effects and were excluded from the analysis. Therefore, we included in the analysis only the observations (countries and years) that indicate administration of Hib and HepB vaccines prior to the introduction of pentavalent. This allows the estimation of incremental coverage of vaccines due to the introduction of combination vaccines.

Although the full data set had 195 countries by 2017/2018 (last year of data used), 132 countries included wP-pentavalent vaccines in their immunisation schedule and data on these countries were used in the empirical analysis. For 30 countries, information on a number of relevant variables, including the date of introduction of pentavalent vaccines, was not available in the data set and these countries were excluded from the analysis resulting in 102 pentavalent vaccine-using countries.

Only the countries using wP-pentavalent in the vaccination schedule were included in the empirical model excluding the aP-pentavalent-using countries. The wP vaccines are associated with significantly higher incidence and severity of adverse events compared with the aP vaccines and considering these two vaccine types as perfect substitutes will bias the results. In addition, there are significant differences in the presentation of the two vaccines which affect the method of vaccine administration and delivery. For example, in most cases, whole-cell
vaccines are supplied in multidose vials while aP vaccines are supplied as single dose or in prefilled syringes with Hib as a powder for reconstitution. The differences in vaccine administration approach may also affect coverage of these and other vaccines in the schedule. It should be noted here that a number of countries switched from wP to aP after the introduction of pentavalent vaccines and these countries were not included in the analysis so that the estimation can focus on the effects of wP-pentavalent vaccines only.

The empirical model

For the empirical analysis, a pooled cross-section and time series data set was built with a panel of countries. The year of introduction or adoption of pentavalent vaccines was obtained, and the year of introduction was used to define a variable representing ‘post-pentavalent introduction dummy’. Our statistical approach was based on a linear mixed model as well as a logistic regression model for the analysis of panel data.

The coverage rates of interest of this study were DTP3, HepB3 and Hib3. Assume that the coverage rate of vaccine $i$ in a country $j$ in year $t$ can be written as $V_{ijt}$. The hypothesis being tested is that the introduction of pentavalent vaccine improved the coverage rate of the antigen $i$. In a country $j$, the year of adoption of the combination vaccine can be written as $T_{pj}$ and this information can be used to define a dummy variable $D_{Tj}$ which is equal to 0 if the year $T < T_{pj}$ and equals to 1 if $T \geq T_{pj}$. For example, if the pentavalent vaccine was introduced in a country in 2009, all years prior to 2009 will be assigned a value of 0 and all years since 2009 will be assigned a value of 1.0. This dummy variable simply defines the pre-years and post-years for pentavalent introduction and estimates the shift in the coverage rate due to the introduction of the combination vaccine. If the introduction of pentavalent vaccine improved the immunisation coverage rate, the coefficient of this dummy variable should be positive, after controlling for other relevant variables.

As discussed in the introduction section, countries have seen significant improvements in vaccine coverage since 1980s, in part due to improved knowledge about vaccine-preventable diseases and lowering of barriers for accessing vaccines. Improved access to vaccines and better knowledge is likely to be affected by various social, economic and health system-related factors. Some of these factors are observable while others are not directly observable. In general, we can write these other factors as $Z_{jt} = \{Z_{1jt}, Z_{2jt}, \ldots, Z_{mtj}\}$. In the empirical model, we can also incorporate a time trend $Y$ to reflect general time-dependent changes.

Therefore, the empirical model for explaining vaccine coverage rates should be:

$$V_{ijt} = f([Z_{jt}], Y, D_{Tj})$$

Since the factors in the vector $[Z_{jt}]$ as well as time trend $Y$ should affect the coverage rates of all vaccines, the effects of these factors can be controlled if it is possible to identify proxy variables that reflect these underlying macro-level changes. One option would be to use the coverage rates of vaccines that are unlikely to be affected by the introduction of combination vaccines. The coverage rates of vaccines against BCG and measles are not directly related to the pentavalent and we can consider these as the proxy variables for vector $[Z_{jt}]$ and $Y$. Even though these variables are not perfect controls for unobservable, coverage of these two vaccines probably represents the best proxies available.

In general, the recommended age for BCG (Bacillus Calmette–Guérin) and measles-containing vaccines (MCVs) does not coincide with the recommended ages for pentavalent vaccine administration (usually 6, 10 and 14 weeks), and the coverage of these two vaccines should not be directly related to the adoption of pentavalent vaccines. The WHO recommends BCG as one of the first vaccines to be given shortly after birth and the MCV is usually administered in between 9 and 12 months depending on the measles-associated morbidity of a country. If the vaccine delivery system and infrastructure improve or if there is general improvement in vaccine-related knowledge among the population, coverage of both these vaccines should increase. Therefore, coverage rates of measles and BCG vaccines can be used as proxy variables to capture the effect of observable and unobservable factors affecting vaccine coverage in general. Using the coverage rates of both BCG and measles as proxy for the variables $[Z_{jt}]$ as well as for $Y$, the final empirical model, after replacing the set of vectors in $[Z_{jt}]$ and $Y$ by coverage rate of measles and BCG, becomes:

$$V_{ijt} = f(V_{Mjt}, V_{Bjt}, D_{Tj})$$

where $V_{Mjt}$ and $V_{Bjt}$ are the coverage rates of measles and BCG vaccines in country $j$ for the year $t$.

In the mixed-effect model, random effect was limited to intercept and the estimated linear equation can be written for the antigen $i$ as:

$$V_{ijt} = \beta_1 V_{Mjt} + \beta_2 V_{Bjt} + \beta_3 D_{Tj} + u_{ij} + v_{ijt}$$

where $u$ is the random effect and $v$ is the pure residual. The $V_{Mjt}$ and $V_{Bjt}$ are the coverage rates of measles and BCG, respectively, and inclusion of one or both variables in the model will be guided by empirical performance of the estimated equations. For linear mixed models, conditional Akaike information criterion (cAIC) can be used to select variables in order to improve inference for the outcome variable. In this study, cAIC values will be used to decide whether to include $V_{Mjt}$ or $V_{Bjt}$ or both in the models. We also calculated the root mean square error (RMSE) for each of the models considered. In addition to statistical results, a graph was generated to compare the predicted annual coverage of vaccines with the average of annual observed coverage. Scatter plots for observed versus predicted were also used to visually evaluate the goodness of fit of the empirical models.

Data analysis

The analysis was performed with R V.4.0.4 and RStudio using the lme4 package and the cAIC package. The R
code and data used for generating the results presented in this article are available in an online repository (https://gitlab.com/SPMEGModels/pentavalent_coverage.git).

**Patient and public involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**RESULTS**

Table 1 compares the characteristics and geographical locations of all countries using wP-pentavalent and the countries in our DTP coverage model. Since the EPI introduced the DTP as one of the vaccines in 1970s, almost all countries should be in the DTP coverage model except those with missing BCG or measles coverage information. As expected, the proportion of high-income countries declines from 29.7% to 12.1% when only the countries using wP-pentavalent were selected. Relative importance of high-income countries further declines (and importance of low income and lower middle income increases) when countries with wP-pentavalent as well as no missing information on BCG, measles and year of adoption of pentavalent were considered.

As indicated in the Methods section, analysis of vaccine coverage due to introduction of combination vaccines used data only for the countries and years where/when the target vaccines existed prior to the introduction of wP-pentavalent vaccines, and other relevant variables like coverage of BCG and measles vaccines were available for these countries. Table 2 reports the characteristics of the countries that satisfy the inclusion criteria for the HepB and Hib vaccine coverage models. Of the 132 countries, 67 and 17 countries adopted HepB and Hib, respectively, prior to the introduction of...

| Characteristics of countries | All countries in the data set | Countries using wP-pentavalent vaccines | Countries in the DTP coverage model |
|-----------------------------|--------------------------------|----------------------------------------|-------------------------------------|
| Total number of countries   | 195                           | 132                                    | 102                                 |
| Income levels of countries (% of total) |                |                                        |                                      |
| Low income                  | 17.4                          | 25.8                                   | 33.3                                 |
| Lower middle                | 24.1                          | 34.1                                   | 37.2                                 |
| Upper middle                | 28.7                          | 28.0                                   | 22.5                                 |
| High income                 | 29.7                          | 12.1                                   | 6.9                                  |
| **TOTAL**                   | **100.0**                     | **100.0**                              | **100.0**                            |

| Geographical location of countries (% of total) | | |
|-------------------------------------------------|----------------------------------------|-------------------------------------|
| Africa                                          | 24.1                                   | 34.1                               |
| Americas                                        | 17.9                                   | 23.4                               |
| Eastern Mediterranean                           | 10.8                                   | 12.9                               |
| Europe                                          | 27.7                                   | 9.8                                |
| South-East Asia                                 | 5.6                                    | 8.3                                |
| Western Pacific                                 | 13.8                                   | 11.4                               |
| **TOTAL**                                       | **100.0**                              | **100.0**                          |**100.0** |

DTP, diphtheria, tetanus, pertussis; wP, whole-cell pertussis.

| Characteristics of countries | Countries in HepB coverage model | Countries in Hib coverage model |
|-----------------------------|----------------------------------|--------------------------------|
| Total number of countries   | 67                               | 17                             |
| Income levels of countries (% of total) |                |                                        |                                      |
| Low income                  | 28.3                              | 17.6                            |
| Lower middle                | 44.7                              | 17.6                            |
| Upper middle                | 20.9                              | 41.2                            |
| High income                 | 6.0                               | 23.5                            |
| **TOTAL**                   | **100.0**                         | **100.0**                       |

| Geographical location of countries (% of total) | |
|-------------------------------------------------|----------------|
| Africa                                          | 32.8          |
| Americas                                        | 14.9          |
| Eastern Mediterranean                           | 13.4          |
| Europe                                          | 11.9          |
| South-East Asia                                 | 14.9          |
| Western Pacific                                 | 11.9          |
| **TOTAL**                                       | **100.0**     |**100.0** |

HepB, hepatitis B; Hib, Haemophilus influenzae type B; wP, whole-cell pertussis.
wP-pentavalent vaccines. Within these countries, only the years in which HepB and Hib were used were included in the analysis. For both HepB and Hib models, relative importance of low-income countries declined compared with the DTP model. The Hib sample becomes predominantly high-income and upper middle-income countries. In terms of geographical locations, more than half of the Hib vaccine-using countries in the data set were in the Americas and Western Pacific. Eastern Mediterranean accounted for about one-third of the countries in the sample.

Using the observations as described in tables 1 and 2, mixed-effect regression models as well as logistic models were estimated for the pooled cross-section and time series data. Table 3 reports the results for DTP. The effect of introduction of combination vaccines is shown by the shifter variable, the dummy for post-pentavalent introduction years. Different combinations of proxy variables (coverage of BCG alone, first dose of MCV (MCV1) alone and both BCG and MCV1) were evaluated as a mechanism for capturing changes in the immunisation programmes or longer-term changes in access and vaccine knowledge. Model selection using cAIC suggests that the inclusion of both the proxy coverage variables performed better than other alternatives.

Table 3 indicates that the introduction of wP-pentavalent vaccines increased the DTP3 coverage by about 3 percentage points (95% CI 2.45 to 3.61%). Therefore, introduction of pentavalent vaccines had statistically significant impact on vaccine coverage rates of DTP3, although the incremental effects were quite small but still important because the coverage of DTP appears to have stalled in recent years. To examine how well the empirical model predicts the coverage of DTP3 in countries, figure 1 shows the estimated and observed coverage rates by year. Note that the model predicts the actual coverage of DTP3 very well. The corresponding scatter plot of observed versus predicted is presented in online supplemental figure S2.

Table 4 reports the results for HepB3 and Hib3 coverage rates and the incremental effect of introducing the combination vaccines. The post-pentavalent year dummy indicates that the incremental effect of the combination vaccines was to increase coverage of HepB3 by 10.1 percentage points (95% CI 8.41% to 11.71%) and the coverage of Hib3 by 9.9 percentage points (95% CI 7.08% to 12.71%). The increase in coverage was not due to the introduction of two new antigens in the schedule (HepB and Hib) but to its inclusion as part of the pentavalent vaccine. The figures corresponding to observed versus predicted based on annual average and for each data point are presented in online supplemental figures S3–S6.

DISCUSSION

This study examined the effect of combination vaccines on childhood vaccine coverage rates from the global perspective, that is, considering all countries where wP-pentavalent vaccines were introduced (subject to availability of required data). To our knowledge, this is the first study that has conducted such an analysis at the global level.

The results imply that the introduction of pentavalent vaccines was associated with increased coverage of DTP3, HepB3 and Hib3. The DTP vaccines were introduced in the immunisation programmes in 1970s and it reached a relatively high coverage rate by 2000. Since then, worldwide coverage of DTP3 has stagnated. The positive impact of pentavalent introduction on DTP3 coverage...
suggests that combination vaccines may have helped in improving DTP3 coverage although other variables such as the strengthening of health systems may have also played an important role. Our analyses found that the introduction of pentavalent vaccines was associated with increased coverage of DTP3 by about 3 percentage points over and above the coverage increase of other vaccines not delivered at the same time as the DTP doses in the schedule. Increased coverage of the ‘proxy’ vaccines should reflect improvements in immunisation infrastructure, economic growth, enhanced access and improved vaccination-related knowledge of the population across countries and over the years. Although the increase in coverage of DTP3 is quite small in quantitative terms, it is still significant considering that global annual increase in DTP3 coverage of 0.9% (varying from 0.1% to 1.8% over the years by WHO regions) for the years 2000 and 2009.\textsuperscript{37} Despite this modest effect of combination vaccines on DTP3 coverage, it will still be helpful in reaching the target coverage rate of 90%. Only about 66% of countries have been successful in achieving the target by 2018,\textsuperscript{38} implying that introduction of combination vaccines may be considered as a potential strategy in achieving and sustaining the target coverage rates for major childhood vaccines.

The estimates of coverage increase of combination vaccines on new and underused vaccines are quite large. After controlling for coverage due to the introduction of new antigens through pentavalent vaccines, the combination vaccines itself helped improve the coverage rates of HepB3 and Hib3 by about 10 percentage points. Immunising against HepB and Hib prior to the introduction of pentavalent vaccines, in most cases, required separate injections in addition to DTP and IPV injections, and introduction of these new shots may have discouraged increased coverage.\textsuperscript{39,40} With the introduction of pentavalent, these antigens could be delivered through a single shot.

The results agree with earlier studies that found positive effect of combination vaccines at country and region level and it implies that the positive incremental coverage effects may be valid at the global level as well. Higher coverage of vaccines due to the introduction of combination vaccines may be explained by the lowering (or not increasing) of the number of injections required in a single visit, higher number of antigens delivered and simplification of vaccination schedule by removing the complexity of dealing with multiple vaccines and multiple shots at the same time. Administering multiple shots during the same visit may also increase programmatic errors (maladministration, delayed administration, etc) as has been reported elsewhere.\textsuperscript{14} For antigens being used for many years prior to the introduction of combination vaccines, the effect on coverage is modest but still significant. Currently, there are various hexavalent wP (DTwP–IPV–HepB–Hib) vaccines being developed which will include IPV in addition to the existing antigens in the pentavalent.\textsuperscript{20–23} This aligns well with the WHO recommendation of including at least one dose of IPV worldwide. The empirical results of this research imply that the introduction of wP-hexavalent vaccine will likely improve the coverage of IPV compared with IPV as a standalone. Such combination vaccines will also help sustain the high coverage of polio vaccination in the longer run worldwide.

The study has various limitations. Although the data quality used in the analysis is presumed to be good, there are still few missing data on vaccine coverage. The number of missing values, however, is not large enough to create estimation problem. For this study, information on the year of introduction of wP-pentavalent vaccines was collected from various sources including Gavi; but for a limited number of countries, the year of introduction of pentavalent vaccines was found to be inconsistent with the vaccine coverage data on HepB and Hib. For our analysis, we have used WHO/UNICEF-reported coverage rate to redefine the year of introduction of pentavalent

### Table 4 Estimated effect of wP-pentavalent vaccine introduction on HepB3 and Hib3 coverage rates

| Independent variables | Coverage of HepB3, % (95% CI) | Coverage of Hib3, % (95% CI) |
|-----------------------|--------------------------------|--------------------------------|
| Constant              | −12.708 (−23.489 to 1.927)    | −51.678 (−84.217 to 19.138) |
| MCV1                  | 0.808 (0.690 to 0.926)        | 0.501 (0.212 to 0.790)       |
| BCG                   | 0.216 (0.056 to 0.376)        | 0.908 (0.520 to 1.296)       |
| Pentavalent Introduction year dummy (=1 in post-penta years) | 10.061 (8.409 to 11.714) | 9.894 (7.079 to 12.709)       |
| Number of countries   | 67                            | 17                            |
| Number of observations | 1290                          | 308                           |
| Log-likelihood        | −5239.2                       | −1177.1                       |
| Conditional AIC       | 10.445.99                     | 2343.94                       |
| Root mean square error| 15.19                         | 10.22                         |

AIC, Akaike information criterion; HepB3, third dose of hepatitis B; Hib3, third dose of Haemophilus influenzae type B; MCV1, first dose of measles-containing vaccine; wP, whole-cell pertussis.
for countries that did not use HepB and/or Hib prior to pentavalent. Despite this, it is still possible that the year of introduction of pentavalent vaccines may not be correct for a small number of countries. In this paper, the conclusions are based on the results of the linear regression model although some authors prefer to use logistic regression when the continuous dependent variable is bounded in between 0 and 100. The case against linear models in such situations is not as strong as often assumed. For comparative purposes, the logistic model was also run and the results are presented in online supplemental table S1, figures S7 and S8. In the linear model, only about 3% of predicted values fell beyond the range (0–100) and the measure of ‘fit’ of the linear model was better than the logistic model (measured by RMSE). In any case, logistic model shows very similar results as the linear model in terms of effect of introduction of pentavalent vaccine on coverage rates of DTP3, HepB3, and Hib3. Interpreting the coefficients of linear model is also easier than interpreting logistic function coefficients. The fourth limitation is the ‘reduced’ number of sample countries and years in the data set for the estimation of HepB and Hib coverage equations. The reduced sample size lowered the relative importance of low-income countries in the data set. The HepB coverage model was based on 67 countries while the Hib coverage model had only 17 countries. If the number and country characteristics create any bias in the empirical estimation, the bias should be lower for HepB. The estimates suggest that the incremental coverage effect of both HepB and Hib was probably about 10 percentage points suggesting that the potential bias, if any, is likely to be very small. Another limitation of the study is related to Gavi support to countries. Even though Gavi funding introduced pentavalent vaccine in many of the countries in the sample, the assistance Gavi provided went beyond vaccine procurement and enhanced vaccine infrastructure and delivery. If these structural changes were more specific to pentavalent vaccine delivery, a part of coverage increase could be attributed to Gavi support. A final limitation is that this study could not include the effect of shift from tetravalent (DTwP–Hib or DTwP–HepB) vaccines to pentavalent due to lack of relevant information.

CONCLUSION

In conclusion, the empirical estimates suggested that combination vaccines may have helped in increasing the coverage rates of existing antigens in the national immunization programmes and the effects are larger for relatively new vaccines (eg, HepB and Hib) than the vaccines that have been in place for many years (eg, DTP). Even though DTP3 achieved a relatively high coverage rate prior to the introduction of pentavalent, the combination vaccines appear to have improved global coverage by about 3 percentage points. The results imply that for achieving a high coverage rate of vaccines, policymakers should emphasise inclusion of vaccines in a combination rather than introducing the vaccines in standalone format. Introduction of combination vaccines can potentially generate other positive outcomes not considered here in this study. Future research should try to estimate the effects of combination vaccines in reducing intracountry inequality in vaccine coverage as well as timeliness of vaccine administration.
Khan MM, et al. BMJ Open 2022;12:e053236. doi:10.1136/bmjopen-2021-053236

3 WHO. Global burden of disease 2000: version 1 estimates, 2001. Available: https://www.who.int/healthinfo/global_burden_disease_estimates_regional_2000_v1/en/ [Accessed 11 June 2022].

4 Gavi, The Vaccine Alliance. Gavi@20: The story of an Alliance that today protects half of the world’s children, 2020a. Available: https://www.gavi.org/gavi-at-20 [Accessed 09 Mar 2020].

5 Gavi, The Vaccine Alliance. Pentavalent vaccine support, 2020. Available: https://www.gavi.org/types-support/vaccine-support/pentavalent [Accessed 31 Jan 2020].

6 Otowa S, Clark S, Suppo J, et al. Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001-2020. Bull World Health Organ 2017;95:629–38.

7 Malhame M, Baker E, Gandhi G, et al. Shaping markets to benefit global health - A 15-year history and lessons learned from the pentavalent vaccine market. Vaccine X 2019;2:100033.

8 Macartney K, Gidding HF, Trinh L, et al. Evaluation of combination Measles-Mumps-Rubella-Vaccinia vaccine introduction in Australia. JAMA Pediatr 2017;171:992–8.

9 Wutzler P, Nell A, Banz K, et al. Can varicella be eliminated by vaccination? Potential clinical and economic effects of universal childhood varicella immunisation in Germany. Med Microbiol Immunol 2002;191:89–96.

10 Rentier B, Gershon AA, European Working Group on Varicella. Consensus: vaccination against varicella—a challenge for Europe. Pediatr Infect Dis J 2004;23:379–89.

11 Happe LE, Lunacek OE, Marshall GS, et al. Combination vaccine use and vaccination quality in a managed care population. Am J Manag Care 2007;13:506–12.

12 Meyerhof S, Clark S, Suppo J, et al. Impact of a pentavalent combination vaccine on immunization timeliness in a state Medicaid programme. Pediatr Infect Dis J 2009;28:98–101.

13 Ramet J. A new challenge for Europe: introducing a pediatric quadrivalent vaccine for measles, mumps, rubella, and varicella. Int J Infect Dis 2005;9:S61–2.

14 Maman K, Zöllner Y. The value of childhood combination vaccines: from beliefs to evidence. Hum Vaccin Immunother 2015;11:2132–41.

15 Smith LE, Amlöt R, Weinman J, et al. A systematic review of factors affecting vaccine uptake in young children. Vaccine 2017;35:6059–69.

16 Meyerhoff AS, Jacobs RJ. Do too many shots due lead to missed vaccination opportunities? does it matter? Prev Med 2005;41:540–4.

17 WHO. Global vaccine action plan 2011-2020. Available: http://www.who.int/immunization/monitoring_surveillance/data/coverage_estimates_series.xls?ua=1 [Accessed 01 Dec 2019].

18 World Bank. Data bank: world development indicators, 2020. Available: https://databank.worldbank.org/source/world-development-indicators.

19 Patterson J, Kagina BM, Gold M, et al. Comparison of adverse events following immunization with acellular and whole-cell pertussis vaccines: a systematic review. Vaccine 2018;36:8007–16.

20 Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med 1997;16:2349–80.

21 WHO recommendations for routine immunization - summary tables, 2019. Available: https://www.who.int/immunization/policy/immunization_tables/en/ [Accessed 01 Dec 2019].

22 WHO. Measles vaccine: WHO position paper – April 2017. Wkly Epidemiol Rec 2017;92:205–28.

23 SGAfT K. On the behaviour of marginal and conditional Aic in linear mixed models. Biometrika 2010;97:773–89.

24 R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2013. Available: http://www.R-project.org/.

25 RStudio Team. R Studio: integrated development for R. Boston, MA: R Studio, Inc, 2015. Available: https://www.rstudio.com/.

26 Bates D, Mächler M, Bolker B, et al. Fitting Linear Mixed-effects Models Using lme4. J Stat Softw 2015;67:1–48.

27 Wallace AS, Ryman TK, Dietz V. Overview of global, regional, and national routine vaccination coverage trends and growth patterns from 1980 to 2009: implications for vaccine-preventable disease eradication and elimination initiatives. J Infect Dis 2014;210 Suppl 1:S5S1–22.

28 Peck M, Gacic-Dobos M, Diolto MS, et al. Global routine vaccination coverage, 2018. MMWR Mortal Mortal Wkly Rep 2019;68:937–42.

29 Lane S, MacDonald NE, Marti M, et al. Vaccine hesitancy around the globe: analysis of three years of WHO/UNICEF joint reporting form data-2015-2017. Vaccine 2018;36:3861–7.

30 Salmon DA, Dudley MZ, Glanz JM, et al. Vaccine Hesitancy: causes, consequences, and a call to action. Am J Prev Med 2015;49:S391–8.

31 Hellevik O. Linear versus logistic regression when the dependent variable is a dichotomy. Qual Quant 2009;43:59–74.