Evaluation of the Effectiveness of *Haemophilus influenzae* Type b Conjugate Vaccine Introduction against Radiologically-Confirmed Hospitalized Pneumonia in Young Children in Ukraine

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Objective *Haemophilus influenzae* type b (Hib) conjugate vaccine was included into the national vaccination schedule of Ukraine in 2006. The objective of this study was to demonstrate the effectiveness of Hib conjugate vaccine against radiologically-confirmed hospitalized pneumonia in children.

Study design Children <2 years old with radiologically confirmed pneumonia admitted to 11 participating hospitals in Kiev and Dnepropetrovsk between April 2007 and June 2009 were included in a case-control evaluation. Four controls were matched to each case by date of birth (within 14 days) and outpatient clinic. We estimated ORs for vaccination and vaccine effectiveness ((1 − OR)*100%) using conditional logistic regression, adjusting for comorbid conditions and contraindications for vaccination.

Results We enrolled 188 case-children and 735 controls. Median age was 16 months (range 4-24 months). Fifty-one percent of cases and 67% of controls received ≥1 doses of Hib conjugate vaccine; 26% of cases and 37% of controls received ≥3 doses. The effectiveness of ≥1 dose Hib conjugate vaccine was estimated at 45% (95% CI 18%-63%).

Conclusions Our study showed that Hib infections are important causes of hospitalized radiologically confirmed pneumonia in young children in Ukraine. *(J Pediatr 2013;163:S12-8)*.

In the absence of vaccination, *Haemophilus influenzae* type b (Hib) is a leading cause of bacterial meningitis and pneumonia among young children. Despite the existence of an effective vaccine, Hib infections were responsible for an estimated 371 000 of the nearly 2 million pneumonia deaths worldwide among children <5 years in 2000.[1] Hib conjugate vaccines have demonstrated efficacy in developing country settings,[2-4] and routine childhood immunization against Hib disease has led to its near elimination in both developing and industrialized countries.[5-9] The World Health Organization (WHO) recommends the introduction of Hib conjugate vaccines into all routine childhood immunization programs.[10] Although uptake of Hib conjugate vaccine in developing countries has increased with support from the GAVI Alliance,[11,12] data are still needed on the impact of vaccination to help sustain its use.

Lack of awareness of the importance of Hib as a cause of severe pneumonia and death in young children has delayed uptake of Hib conjugate vaccines in developing countries. The etiology of pneumonia is not routinely determined in clinical practice because of low sensitivity of culture methods, widespread use of antibiotics prior to health center visits, and limited laboratory capacity in low-resource countries. A meta-analysis of randomized, controlled trials of Hib conjugate vaccines estimated that Hib causes 5% of clinical pneumonia episodes in young children and 21% of episodes with radiological consolidation on chest radiographs.[1] In Eastern Europe, although pneumonia and acute respiratory infections are recognized as leading postneonatal causes of early childhood death,[13] there was little perception of Hib disease burden prior to the introduction of Hib conjugate vaccines.

In 2006, the government of Ukraine introduced Hib conjugate vaccine into its routine childhood immunization schedule based on the documented effectiveness and safety of the vaccine in developed countries and a desire to harmonize the immunization schedule with countries of Western Europe. Ukraine was the first country in the region to adopt Hib conjugate vaccine, and WHO considered documentation of the impact of vaccination a priority for the regional uptake of Hib conjugate vaccine and its sustainability. We report here on a case-control study of

DTaP	Diphtheria-tetanus-acellular pertussis
DTP	Diphtheria-tetanus-whole cell pertussis
Hep B	Hepatitis B
Hib	*Haemophilus influenzae* type b
WHO	World Health Organization

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Hib conjugate vaccine effectiveness against radiologically confirmed pneumonia among children <2 years of age in Ukraine.

Methods

The total population in Ukraine is 46 million, with the population under 5 years of age estimated at 2.4 million and the annual number of births estimated at 490 000.[14] The study was conducted in two large cities, Kiev and Dnepropetrovsk, with population of 2.7 and 1.2 million, respectively. This study was considered program evaluation by ethical review committees of the Ukrainian Ministry of Health, Centers for Disease Control and Prevention, and WHO and was exempt from human subjects review.

Health System in Ukraine

All children <18 years of age in Ukraine receive routine immunizations and healthcare at a polyclinic, primary healthcare centers, where children are registered based on the residence. Children reporting to polyclinics with clinical symptoms of pneumonia will be referred to pediatric hospitals when a primary care pediatrician determines whether a child with suspected pneumonia should be referred for hospitalization or treated as an outpatient. Although healthcare in Ukraine is free and provided by the government for all citizens and long-term registered residents, parents are often asked to cover a significant portion of expenses associated with nonroutine care, including purchase of antibiotics and medical supplies. Vaccines included in the national Expanded Program on Immunizations are purchased by the government and provided at no cost at polyclinics. Vaccines are also available at private clinics, including vaccines not provided by Ukraine's national immunization program.

Ukraine's National Immunization Program

In 2006, when the government of Ukraine decided to introduce Hib conjugate vaccine into the national immunization program, the infant immunization calendar included a birth dose of Bacille Calmette-Guerin, 2 doses of inactivated polio vaccine at 3 and 4 months, 2 doses of oral polio vaccine at 5 and 18 months of age, 3 doses of diphtheria-tetanus-whole cell pertussis (DTP) at 3, 4, and 5 months plus a booster dose of diphtheria-tetanus-acellular pertussis (DTaP) at 18 months, and 3 doses of hepatitis B (Hep B) vaccine (at birth, 1 and 6 months). Contraindications for all vaccination among children in Ukraine include any acute illness (during which it is recommended to postpone a vaccine dose), anaphylaxis, severe adverse reaction to previous doses of the vaccine, allergies to any vaccine component, and epilepsy (with 2 or more seizure episodes per month).[15] Vaccination cards are updated and kept at the polyclinic where a child is registered. In case of residence change, vaccination records along with the health records are transferred to a polyclinic associated with a new residence.

In June 2006, the Ministry of Health of Ukraine introduced 2 monovalent Hib conjugate vaccines (Hiberix [PRP-T]; GlaxoSmithKline, Middlesex, United Kingdom and ActHib [PRP-T]; Sanofi Pasteur). The national vaccination schedule recommended 3 doses of Hib conjugate vaccine administered at 3, 4, and 5 months of age, at the same time as DTP. Two doses were recommended for children who were already 6-12 months of age and had already received their first or second dose of DTP. However, the extent to which this catch-up schedule was implemented is unknown. Beginning in 2007, the government of Ukraine purchased additional doses of monovalent Hib conjugate vaccine to provide a booster dose to all children in the 2006 birth cohort during their second year of life. In 2007-2008, the government purchased a tetravalent DTaP-Hib conjugate vaccine (TetraHib, Sanofi Pasteur) for routine use in infants. Polyclinics report on a quarterly basis to local and central health authorities the number of children eligible to receive each dose of the recommended vaccines and the number of children vaccinated. The coverage estimates are compiled at the Ministry of Health and reported quarterly. According to coverage estimates reported by Ukraine Ministry of Health, 11% of eligible children <12 months of age had received 3 doses of Hib conjugate vaccine in 2006. The reported coverage increased to 80.6% in 2008 and 76.4% in 2009. The coverage of 3 or more doses of DTP was reported to be 90% in 2008 for the same age group.

Identification of Hospitalized Pneumonia Episodes with Radiologic Confirmation

Case-patients for this evaluation were children admitted to 7 public hospitals in Kiev and 4 public hospitals in Dnepropetrovsk between April 1, 2007 and June 30, 2009. The hospitals were selected for participation if they admitted young children with pneumonia and if chest radiographs were routinely obtained for children with suspected pneumonia. Children with clinically suspected pneumonia were prospectively identified from hospital admission or discharge logs. Clinical suspicion was based on findings of physical examination and auscultation. Children 4-23 months of age hospitalized with radiologically confirmed pneumonia who were eligible to receive Hib conjugate vaccine (ie, born after June 1, 2006) and who had vaccination and medical records available for review were included in this evaluation. Hospital charts were reviewed and standard case report forms completed for eligible case-patients to record information on clinical presentation, course of the illness, and results of chest radiograph reading. The underlying medical conditions of interest were systemic steroid use, congenital heart disease, respiratory system pathology, cystic fibrosis, immune deficiency, HIV, asplenia, cancer, and low birthweight (<2500 g). Children hospitalized for a pneumonia episode who did not meet the definition of radiologically confirmed pneumonia were excluded from this evaluation, as were case-patients who resided outside Kiev and Dnepropetrovsk.

Interpretation of Chest Radiographs

We used the standard WHO criteria for interpreting chest radiographs and diagnosing pneumonia.[16] In 2006, prior to study initiation, a training workshop was organized for

pediatricians and radiologists of Kiev pediatric hospitals to standardize interpretation of radiographs for the diagnosis of radiologically confirmed pneumonia.

Chest radiographs were read independently by a pediatrician and a radiologist. Both readers completed the self-assessment training for standardization of radiograph interpretation for defining radiologically confirmed pneumonia according to WHO criteria. We found 98% concordance in positive readings between the 2 readers. The remaining discrepancies (2%) found between the 2 readings were resolved by a third reading conducted by a senior pediatric radiologist. In addition, a 20% sample of concordant readings was evaluated by a senior radiologist for quality assurance.

Control Selection

For each case-patient, up to 4 age-matched children were identified from among those registered at the same polyclinic as the case-patient. First, polyclinic registers were searched to create a list of potential control-children born within 14 days of the case-patient's date of birth. From this list, 4 potential control children were randomly selected by drawing numbers. Information on Hib and other childhood vaccinations, presence of underlying comorbid conditions (same as those evaluated for case-patients), and prior antibiotic use for both cases and matched controls was obtained from medical charts and individual vaccination cards maintained at polyclinics for all children residing within the polyclinic catchment area. Control-children with a recorded hospitalization for pneumonia within the last year were excluded and were replaced by drawing another number from the list of potential controls.

Sample Size Calculation

We based our sample size calculations on the number of case-patients and control children needed to detect an effect if the true OR was 0.70 or less, corresponding to a vaccine effectiveness of 30% against radiologically confirmed pneumonia based on findings of previous studies. Assuming 70% vaccination among case-patients, 80% power, and unmatched analysis, 408 cases and 1632 matched controls were required to demonstrate significant effectiveness (upper limit of OR <1.0) if the true OR was 0.7 or less.

Data Analyses

We performed data analysis using SAS v. 9.2 software (SAS Institute, Cary, North Carolina). We estimated an OR of vaccination among case-patients compared with age-matched control children. The effectiveness of Hib vaccination against radiologically confirmed pneumonia was estimated as 1 − (OR for vaccination).[17]

We calculated ORs and 95% CIs using conditional logistic regression models. The primary analysis included vaccine status for children who have received 1or more doses versus no dose of the Hib conjugate vaccine. A dose of the vaccine was valid and was included in the analysis if it was administered at least 14 days before the onset of illness for the case-patient and for the corresponding matched control. In addition, we evaluated vaccine effectiveness among children receiving a single dose or two doses of Hib conjugate vaccine before 7 months of age, and for children receiving three or more doses. We did not have the statistical power to evaluate individual vaccination schedules separately. Because underlying medical conditions and contraindications were associated with vaccination status and disease, we adjusted for presence of underlying medical conditions in all models.

Results

During the study period, we identified 2139 children 4-23 months of age with clinically suspected pneumonia admitted to participating hospitals. All of the children (100%) with suspected pneumonia had chest radiographs available for review. Chest radiographs from 221 pneumonia episodes (10.3% of 2139 episodes among eligible children) were classified as radiologically confirmed pneumonia according the WHO criteria. Among children with radiologically confirmed pneumonia, 64% (140) had a diagnosis of pneumonia recorded on admission, 38 (17%) had bronchitis, and the remaining 43 (19%) had other admission diagnoses (otitis media, laryngitis, laryngotracheitis, ethmoiditis, and sinusitis). Outpatient charts and vaccination records could not be located for 33 (15%) of the children meeting the case definition. The remaining 188 (85%) cases were included in this evaluation. Clinical characteristics of 221 children with radiologically confirmed pneumonia and children included in the case-control evaluation are presented in Table I.

A total of 735 control children were identified through polyclinic records and matched to case-patients with radiograph confirmed pneumonia; we identified 4 controls for 177 (94%) case-patients and 2 or 3 controls for 11 case-patients. Distribution of age and sex was similar among case- and control-children (Table II). Comorbid chronic or immunocompromising conditions were significantly more common among case- versus control-children. Comorbid conditions most frequently identified included congenital heart disease (6% of cases and 3% of controls), birthweight <2500 g (8% of cases and 2% controls), and HIV or other immune deficiency (3% of cases and 1% of controls). Among children with information available in the chart, case-children were more likely than matched controls to have been prescribed antibiotics in the 30 days prior to the date of case-patient's hospitalization (12 [16%] of 68 case-children vs 4 [2%] of 221 control-children [$P < .01$]). Fifty-one percent of cases and 67% of controls ($P < .001$) received ≥1 Hib doses; a higher proportion of controls than cases received ≥3 doses of Hib or ≥1 doses of other childhood recommended vaccines (Table II). A higher proportion of case- than control-children were unvaccinated due to contraindications or parent refusals, as recorded in outpatient charts.

The effectiveness of ≥1 doses of Hib conjugate vaccine was 45% (95% CI 18%-63%) when adjusted for presence of comorbid conditions and contraindications (Table III). The effectiveness was lower among children with comorbid

Table I. Clinical characteristics of children with radiologically-confirmed pneumonia identified at participating hospitals between April 1, 2007 and June 30, 2009

Clinical characteristics	All children meeting the case definition, N (%) N = 221	Children included in the case-control evaluation, N (%) N = 188
Fever (>38°C)	138 (65%)	95 (53%)
Cough	211 (96%)	178 (95%)
Difficulty breathing	158 (72%)	136 (72%)
Dull sounds on percussion	150 (68%)	126 (67%)
Rhonchi on auscultation	122 (55%)	103 (55%)
Cyanosis	87 (39%)	76 (40%)
Chest wall indrawing	83 (38%)	72 (38%)
Diminished breath sounds on percussion	85 (38%)	71 (38%)
Crepitations	47 (21%)	35 (19%)
Tachypnea	31 (14%)	27 (14%)
Length of hospitalization, d (mean/median)	11 (14)	11 (14)
Outcome (death)	2 (1%)	2 (1%)

conditions compared with healthy children; however, CIs for these estimates overlapped. Compared with no vaccine, the point estimate for effectiveness of 3 or 4 doses when given on an infant schedule was higher than for infant schedules with 1 or 2 doses, with widely overlapping CIs (Table III).

Discussion

This study evaluated the impact of routine Hib vaccination on pneumonia in young children in the GAVI-eligible countries of the European region, in which the burden of Hib pneumonia has not been well documented. We found that hospitalized children <2 years of age with radiologically confirmed pneumonia were significantly less likely to have been vaccinated against Hib disease than age-matched children registered at the same primary care center, or polyclinic. The study suggests that Hib is an important contributor to severe pneumonia in young children in Ukraine, specifically to episodes meeting the WHO definition of radiographically-confirmed pneumonia. The high percentage of parent refusals and provider-report of contraindications to vaccination indicate need for improved communication to increase uptake of Hib conjugate vaccines.

Blood cultures are not routinely obtained from children with suspected pneumonia and no data are available on the contribution of Hib infection to this clinical syndrome in Ukraine or countries from this region. Studies evaluating the culture results of lung aspirates from patients with pneumonia showed a wide variation in the proportion of childhood pneumonia due to Hib, indicating that geographic and regional variation may exist.[18] Watt et al conducted a comprehensive review of Hib studies to estimate a global burden of Hib disease, and concluded that Hib contributes 15%-21% of cases of pneumonia.[1] We documented a 45% reduction in

Table II. Comparison of characteristics of cases included in the case-control evaluation and matched controls

Characteristics	Cases (N = 188)	Controls (N = 735)	*P* value*
Age, mo (median, range)	16 (4-23)	16 (4-24)	
Sex (male)	92 (50%)	374 (51%)	.6337
Underlying comorbid conditions†	44 (23%)	70 (10%)	<.0001
Hospitalization for respiratory illness in the previous 6 mo	7/139 (4.7%)	17/551 (3.2%)	.2663
Contraindications for ≥1 recommended vaccine‡	29 (15%)	43 (6%)	<.0001
Parent refusal for ≥1 recommended vaccine	73 (39%)	223 (30%)	.0261
Vaccinations§			
≥1 dose of Hib conjugate vaccine	97 (51%)	494 (67%)	.0001
Hib vaccination status by total number of doses received			
1 dose	25 (13%)	96 (13%)	
2 doses	21 (11%)	126 (17%)	
≥3 doses	51 (27%)	272 (37%)	
≥1 dose of DTaP	123 (65%)	611 (83%)	<.0001
≥1 dose Hep B	125 (67%)	510 (69%)	.5027
Unvaccinated¶	45 (24%)	92 (13%)	.0001
Reasons for not receiving any recommended vaccines:			
Contraindications	16 (9%)	24 (3%)	
Parent refusal	17 (9%)	51 (7%)	
Other reason	12 (7%)	17 (3%)	

*P value for χ^2 test.
†Comorbid conditions evaluated: systemic steroid use, congenital heart disease, respiratory system pathology, cystic fibrosis, immune deficiency, HIV, asplenia, cancer, and low birthweight (<2500 g).
‡Contraindication, as indicated by a primary care provider.
§A dose of the vaccine was included in the analysis if administered at least 14 days before the onset of illness for the case-patient and for the corresponding matched control.
¶Did not receive any of the recommended childhood vaccines.

Table III. Effectiveness of Hib conjugate vaccine against radiologically-confirmed pneumonia by vaccination schedule and presence of comorbid conditions

Vaccination schedule	OR (95% CI)*	Vaccine effectiveness (95% CI)†
≥1 dose of Hib conjugate vaccine		
Overall	0.55 (0.37-0.82)‡	45 (18-63)‡
Healthy children	0.48 (0.32-0.72)	52 (28-68)
Children with comorbid conditions	0.55 (0.25-1.13)	45 (-13-75)
1 or 2 doses <7 months of age	0.51 (0.31-0.84)‡	49 (16-69)‡
3 doses <7 months of age with or without a 4th dose after 12 months of age	0.44 (0.27-0.74)‡	56 (26-73)‡
Other vaccination schedules for children with missed doses	0.49 (0.29-0.85)‡	51 (15-71)‡

*OR for vaccination among cases compared with controls estimated using conditional logistic regression.
†Vaccine effectiveness was calculated as 1 minus OR.
‡Analysis adjusted for the presence of comorbid conditions and contraindications.

radiologically confirmed pneumonia among children younger than 2 years of age vaccinated with 1 or more doses of Hib conjugate vaccine compared with unvaccinated children. Our results are consistent with those of case-control studies of Hib conjugate vaccine effectiveness against radiograph confirmed pneumonia from Colombia,[19] Brazil,[20] and Bangladesh.[21] A meta-analysis suggested that case-control studies tend to overestimate the efficacy of the vaccine against radiologically-confirmed pneumonia compared with efficacy measured in randomized, controlled trials, which are considered the gold standard.[22]

There are several possible reasons for the estimate of vaccine effectiveness in our evaluation being higher than expected. Differences in case ascertainment and interpretation of chest radiographs can contribute to different findings in postvaccine introduction studies. Our evaluation included only cases of hospitalized pneumonia and applied a standardized WHO definition of chest radiograph-confirmed pneumonia, which may have increased the specificity of the outcome and resulted in higher than expected estimate of the effectiveness. Baqui et al reported higher estimates of vaccine effectiveness (33%-44%) against radiologically confirmed pneumonia when the more specific case definition was applied by restricting the analysis to cases confirmed by both WHO and study readers.[21] Chest radiographs in hospitals participating in our evaluation were obtained based on clinical assessment by a physician and differences in clinical indication for obtaining chest radiographs may contribute to differences in point estimates of vaccine effectiveness obtained in different studies. Parent refusals and contraindications also may have confounded our estimates. In our evaluation, case-patients were more likely to have vaccine contraindications reported by a provider than matched controls, and the chart reviews revealed that providers often reported contraindications for children with underlying immunocompromising conditions, which are known to be associated with increased risk of Hib disease and pneumonia. In addition, introduction of Hib conjugate vaccine in Ukraine coincided with an aggressive local mass media antivaccine campaign questioning the safety of childhood vaccines. This may have resulted in parents of children with immunecompromising conditions deciding not to vaccinate their children against Hib disease and may have led to an overestimation of vaccine effectiveness against radiograph confirmed pneumonia. Our data indicate that parents of case-patients were more likely than parents of control children to refuse one or more doses of recommended vaccines, including Hib conjugate vaccine, a finding that may be related to parent education level. Polyclinic records provided a complete source of vaccination history. We matched controls to cases by the polyclinic where children were registered according to their residence district to ensure the selection of controls from the same population from which cases were identified. Even though all children included in this analysis had polyclinic records from which we obtained vaccination histories, migrant families may have limited access to outpatient care, be more likely to utilize hospitals for emergency care, and less likely to be vaccinated, which may have led to oversampling of vaccinated controls. However, we also excluded children with radiologically confirmed pneumonia for whom a valid address, and, consequently, vaccination and polyclinic records were not located.

These findings provide support for the approach of GAVI to accelerate use of Hib conjugate vaccine in the poorest countries. GAVI has supported the introduction of Hib conjugate vaccines in developing countries since 1999. When GAVI was created, the WHO position paper on use of Hib conjugate vaccines recommended their introduction into national immunization programs based on feasibility and disease burden (WHO, 1998). During the first 4 years of GAVI, none of the 8 eligible countries in the newly independent states requested support for introduction of Hib conjugate vaccines, due to concerns about sustainability and lack of data on disease burden. In 2005, GAVI created the Hib Initiative to accelerate introduction of Hib conjugate vaccine.[11] In 2006, WHO revised its position paper to state that local data on Hib disease burden should not delay the introduction of Hib conjugate vaccines into national immunization programs.[10] That same year, the government of Ukraine decided to finance the introduction of Hib conjugate vaccine into the routine childhood immunization schedule. Despite being eligible to receive support from GAVI for vaccine financing, the decision to introduce a monovalent Hib conjugate vaccine without GAVI support was made by policymakers in Ukraine to accelerate the vaccine introduction and allow continued use of locally produced diphtheria-tetanus-whole cell

pertussis (DTP) vaccine. Subsequently, 7 of the 8 GAVI-eligible countries in the European region have switched from DTP-Hep B to pentavalent DTP-Hib-Hep B vaccination due in large part to financial incentives from GAVI.

Although the updated WHO position paper states that disease burden data should not delay Hib introduction, WHO recommends that countries have disease surveillance in place prior to introducing new vaccines to demonstrate impact of vaccination to support the sustainability of the program.[23] Demonstrating the impact of Hib vaccination on culture-confirmed Hib disease in the Ukraine would have strengthened the findings of the case-control study. Ideally, surveillance for Hib should be established at hospitals with microbiology laboratories that can isolate bacterial pathogens, including Hib. However, population-based studies of Hib meningitis and rapid assessments based on WHO protocols have found a low burden of Hib disease in the European region compared with other regions.[24-26] Although lumbar punctures are routinely obtained for children with suspected meningitis, administration of antibiotics prior to hospital admission and limited diagnostic capacity in clinical laboratories throughout the region, including use of expired human blood rather than sheep blood for culture media, limit detection of invasive Hib disease. Blood cultures are not routinely obtained from children with suspected pneumonia and as a result, clinicians in Ukraine have a low awareness of Hib as an etiologic agent of bacterial pneumonia. Therefore, although pneumonia in children is recognized as a public health problem, the importance of Hib vaccination to prevent pneumonia is unappreciated. For this reason, demonstration of an effect of Hib vaccination on radiologically confirmed pneumonia in the Ukraine was particularly important.

Despite limitations inherent to observational studies, post-introduction effectiveness studies are useful to demonstrate the effects of the vaccine in real life settings and benefits of vaccination programs. Public health officials in Ukraine have been concerned about the increasing antivaccine sentiment among parents. In addition, many healthcare providers still do not consider the vaccine a priority because of under-recognition of Hib disease burden. Results of this evaluation support continued use of Hib conjugate vaccines in the region. Prevention of pneumonia needs to be incorporated into strategies to communicate benefits of vaccination against Hib diseases. The findings of this evaluation should have relevance for neighboring countries in the region who may be considering introduction of Hib conjugate vaccine. ■

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Author Disclosures

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