RESEARCH PAPER

Modified Integrated Algorithm for Detection of HIV Among Sick Children Aged 0-14 Year Seeking Care at Healthcare Facilities in India

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Objective: To test the ability and to identify unique criteria in a Modified Integrated Algorithm developed by Indian Council of Medical Research (ICMR) to detect HIV infection among sick children 0 to 14 years, seeking care in a health care facility.

Design: Facility based cross-sectional survey.

Setting: Four talukas of Belgaum District, Karnataka, India during 2013-2014.

Patients: Sick children 0-14 years seeking care at healthcare facilities in the study area.

Procedure: A total of 10 health care facilities were selected using specific criteria. Trained health care providers in these facilities used the WHO generic Integrated Management of Childhood Illnesses screening algorithm for HIV, applicable for children to 0-5 years and ICMR modified integrated algorithm for >5-14 years, to screen and test children for HIV, when they sought care in these facilities.

Main Outcome measure: Prevalence of HIV in children screened positive by the Modified Integrated Algorithm.

Results: Of the total 33342 children who visited the 10 health care facilities, 24342 were screened by the physician. Of the 527 screened positive sick children with suspected signs/ symptoms, 509 consented and were tested with age appropriate HIV testing. 97 children tested positive (HIV prevalence 19.1%: 5% in <5yrs and 28% in ≥5-14 years). The result of Classification and Regression Tree and logistics regression consistently identified parents with HIV and orphan child, as important predictor of HIV infection.

Conclusion: ICMR Modified integrated algorithm may be used as a screening tool in the public and private health care facilities to increase case detection of pediatric HIV.

Keywords: *Diagnosis, Identification, Parents, Tool.*

There is lack of information on the epidemiology of pediatric HIV in India with lack of universal screening for HIV [1]. The HIV case load among children remains unknown as the existing surveillance system in India does not include children. The pediatric burden is estimated/projected to be 6-7% of the adult HIV prevalence [2,3]. Under-diagnosis of pediatric HIV was attributed to the low sensitivity of screening tools at the community level with suggested addition of parental factors to improve the positive predictive value of the Integrated Management of Childhood illnesses- HIV (IMCI-HIV) algorithm [4]. However, this algorithm is applicable to ages up to 5 years only. Children up to 18 years constitute 41% of the total population [5]. Targeted screening of sick children seeking care at healthcare facilities may be possible if the available algorithm is modified for children of all ages. Identification of HIV infection and linkage with anti-retroviral treatment centers would improve child survival among HIV-infected children, currently reported to be less than half of that in adults [6]. This is an important step towards the highly ambitious UN goal of ending AIDS as a public health threat by 2030 [7]. The present study attempted age-appropriate modifications in the generic IMCI-HIV algorithm to create a modified integrated algorithm, and used it to detect prevalence of HIV in sick children 0 to 14 years old.

Accompanying Editorial: Pages 611-12.

METHODS

This cross-sectional study was conducted in four 'talukas' (sub-district administrative regions) of Belgaum District, Karnataka, India *viz*, Athani, Bailhongal, Gokak and Belgaum, during 2013-2014. The study protocol was approved by the ethics committee of St John's Medical

College and Hospital, Bangalore in October, 2012. Informed consent was obtained from caregivers of study participants.

Out of 628 available health care facilities, 113 where HIV testing and care was available were listed by using the following criteria: availability of a physician or a pediatrician, and a case load of at least 30 patients in a month. These 113 HCFs were further categorized into tertiary, secondary and primary, and government and private facilities. Ten facilities were selected by stratified randomization by a person not involved in the study.

WHO generic IMCI screening algorithm [8] for HIV covered children only up to 5 years of age. To extend the algorithm for children up to >5-14 years of age in the study, an ICMR constituted sub-committee suggested modifications in the WHO generic IMCI- HIV algorithm. The sub-committee incorporated features of Integrated Management of Adolescent and Adult Illnesses [9], and a category of conditions common to children of both age categories (0-5 and >5-14) was named as 'other clues for all children' from history suggestive of parental HIV infection. Few symptoms applicable to adolescents were marked with an asterisk, denoting using caution in application, due to the sensitive nature of the questions.

The WHO generic algorithm was used for ages up to 5 years. A child less than 5 years was referred for HIV testing if two or more of the following signs were present: pneumonia or severe pneumonia, persistent diarrhea or severe persistent diarrhea, ear discharge (acute or chronic), very low weight or severe malnutrition, oral thrush, parotid enlargement, and generalized lymphadenopathy.

For 5-14 year ages the Modified integrated algorithm was used. A child 5-14 years old was referred for HIV testing, if any one of the signs given in ***Box* I**, or any sign from the 'other clues' given in ***Box* II**, was present.

A child (aged up to <5 years) satisfying a minimum of two criteria for their age category or one criterion in 'other clues', and a child aged 5-14 years fulfilling a minimum of one criterion in their age category or under 'other clues', was defined as screen positive and referred for age-appropriate HIV testing.

Forty eight physicians/pediatricians posted at 10 healthcare facilities of the study area were trained at the District training centre, to use the Modified integrated algorithm. A post-training feedback evaluation and a weekly visit by the research officer to provide technical and supportive supervision and re-training was done.

Box I Adaptation from Integrated Management of Adolescent and Adult Illnesses Ages >5-14 years

A child 5 -14 years old should be referred for HIV testing if any one sign is present

1. Repeated Infections
2. Lymphadenopathy (PGL)-painless swelling in neck and armpit
3. Oral thrush or oral hairy leukoplakia
4. Esophageal thrush
5. Weight loss more than 10% without other explanation
6. More than 1 month:-
   - Diarrhea (unexplained)
   - Vaginal candidiasis
   - Unexplained fever
   - Herpes simplex ulceration (genital or oral)
7. *Other sexually transmitted infections
8. *Injecting drug use
9. *Sexually active person with multiple partners living in high HIV-burden area.

**Questions to be asked in a sensitive manner to adolescents only*

Box II 'Other clues' for Suspecting HIV Infection for all Children

A child of any age should be referred for HIV testing if any of the 'other clues' are found during history taking/examination

1. Herpes zoster
2. Skin or mouth conditions which are chronic (>3 mon) or refractory to standard treatment
3. Children with disseminated TB/suspected drug resistant TB (Pulmonary or extrapulmonary)
4. Gum/ mouth ulcers
5. Child has any opportunistic infection or condition listed in WHO stage 4 staging for HIV infected children
6. Children with developmental regression
7. Children with recurrent and persistent seborrheic capitis/dermatitis
8. Children with chronic lung disease

If the history suggests:

9. Unexplained death of parent
10. Orphan child
11. History of blood transfusion
12. Parent with HIV/HIV related illness
13. Parent with high risk behavior/occupation

Tools such as flow-charts, ready-reckoners and diagrams were provided and displayed at each of these facilities.

Children who fulfilled the screening criteria for HIV testing were referred for age-appropriate HIV tests: Children <18 months by DNA PCR, Children >18 months tested by ELISA. Trained counsellors provided pre-test counseling to the parent/guardian. Test results were obtained maintaining anonymity. HIV positive children were referred to the appropriate healthcare facility for care, support and treatment.

Data analyses: Data were entered in Microsoft Office Access. Statistical software SPSS IBM version 22.0 (Armonk, NY: IBM Corp.) was used for univariate and multivariable logistic regression analysis and statistical significance was tested using Wald statistics. Overall fit of the model was tested using Hosmer-Lemeshow Chi-square test with *P*-value >0.05 as the criteria for good fit. HIV prevalence across categories was compared by Chi-square test and mean values were compared by Student *t* test. The following study variables were included for univariate analysis: present status of pneumonia, persistent diarrhea in the past 3 months, ear discharge, history of loss of weight, repeated infection, painless swelling in the neck or armpit, weight loss >10%, diarrhea more than one month, vaginal candidiasis more than one month, presence of herpes simplex ulceration more than one month, oral thrush (or) oral hairy leukoplakia, esophageal thrush, multiple sexual partners, herpes zoster presence, chronic skin or mouth condition, presence of TB, WHO stage 4 condition for HIV children, developmental regression, persistent seborrheic capitis, chronic lung disease, unexplained death of parent, orphan child, blood transfusion history, parent with HIV related illness, and parent with high risk occupation. The variables that were found to be statistically significant at *P*<0.05, were included for multi variable logistic regression analysis.

A Classification and Regression Tree (CART) [10,11] model using Salford Predictive Modeler (SPM) software (evaluation version 8.0) was developed. CART is an exploratory data analysis and builds a tree through recursive partitioning in such a way that the data is successfully split into increasingly homogenous subgroups. In the present analysis, minimum number of observations for each terminal node was set as ≥30. Data collected from all 10 health facilities were included in the model. Children with HIV serology negative were labelled as HIV-negative and serology positive were labelled as HIV-positive.

RESULTS

A total of 33342 children visited the 10 healthcare facilities during the period 24 February, 2014 to 30 June, 2014. Among them, 24342 were screened by trained field investigators and confirmed by physician/pediatricians. Out of 527 sick children screened positive by the modified IMCI-HIV algorithm, 509 (mean age 6.8 y) consented and were tested with age-appropriate HIV tests.

Overall HIV positivity in 0-14 years (*n*=509) was 19.1% (*n*=97) (95% CI 15.7, 22.7); 5% in <5 years and 28% in ≥5-14 years. Age and gender profile of the study population is given in ***Table* I**. There was no significant difference in the age distribution between the genders (*P*=0.3). The mean age of boys was significantly higher than girls (*P*=0.005). HIV prevalence in different taluks is shown in ***Table* II**.

Only 14 out of 22 (64%) criteria in the modified IMCI–HIV algorithm were found to be useful in identifying HIV infected children. Univariate analysis identified eight variables (persistent diarrhea, discharging ear, very low weight, diarrhea, unexplained fever, orphan child, history of blood transfusion and parents with HIV) as significantly associated with HIV status. Final statistical model on multivariable logistic regression yielded three significant variables (unexplained fever, orphan child and parents with HIV); **(*Table* III)**. Using these three variables, correct classification of negatives and positives was 90% and 95%, respectively.

Table I Demographic Profile of Study Population (*N*=509)

Variables	*No. (%)*
Male gender	294 (57.8)
Age group (y)	
<1	15 (2.9)
1-5	196 (38.5)
6-10	182 (35.8)
11-14	116 (22.8)
*Educational status**	
Illiterate	10 (2.0)
Class 1-5	176 (34.6)
Class 6-12	87 (17.0)
Below school going age	233 (45.8)
Occupational status of parents/guardians#	
Daily wage earners	336 (66.0)
Salaried	53 (10.4)
Business	56 (11.0)
Housewife	20 (3.9)
Sex workers	5 (1.0)
Retired and others	11 (2.2)

*Data not available for *3 and #28 respondents.*

WHAT IS ALREADY KNOWN?

- Addition of parental factors to the IMCI-HIV algorithm improves the positive predictive value of the tool applicable for children younger than 5 years in low-resource settings.

WHAT THIS STUDY ADDS?

- A Modified Integrated Algorithm detected high prevalence of pediatric HIV in sick children aged 0-14 years.
- Unexplained fever for more than one month, a HIV-positive parent and being orphan were predictors of HIV infection among sick children in a low-resource and high-burden setting.

CART can statistically demonstrate which factors are particularly important in a model or relationship in terms of explanatory power and variance. Accordingly, these diagnostic measures were compared between logistic and CART model (***Web Table* I**). It was observed that while identifying the children of HIV parents and orphan, overall about 94% of HIV children may be predicted correctly. The diagnostic measure was compared between logistic and CART model which showed similar sensitivity (94.8% and 94%), specificity (90% each) and diagnostic accuracy (91.2% and 91%), respectively for identifying the children with HIV parents and orphans. The area under curve (AUC) is presented in ***Fig*. 1**. Apart from HIV parents and orphan children, presence of unexplained fever was captured as another significant variable in the logistic regression analysis. However, diagnostic measures did not vary significantly. Therefore, 'parents with HIV' and 'orphan child' are important with the order of priority scores being 100% and 50%, respectively as emerged by CART analysis.

DISCUSSION

In this study, the WHO generic IMCI algorithm was modified by addition of components from the Integrated Management of Adolescence and Adult Illnesses and 'other clues' for suspecting HIV infection in children ≥5-14 years. A higher age-specific prevalence of HIV was identified in ≥5 -14 year old children. The positivity rate among adults tested was reported as 2.7 in Belgaum in 2014. The prevalence in 0 - <5 year was similar as estimated from adult HIV projections. Earlier studies [12,13] have reported local adaptation of the WHO generic algorithm in improving diagnosis of pediatric HIV; however, they were limited to ages 0 - <5 years.

Most of the criteria in the Modified integrated algorithm were useful in identifying HIV infected children in this population. Unexplained fever more than one month, being an orphan child and having parents with HIV were the top three predictors of HIV test positivity, with high percent correct classification of negatives and positives unlike eight other common clinical features. Application of this algorithm in similar settings elsewhere should take this into consideration and make deletions in the algorithm based on background

Table II HIV Prevalence in Different Taluks

Taluk	*Study subjects*	*Prevalence, n (%)*
Athani	43	3 (7.0)
Bailhongal	65	2 (3.1)
Belgaum	332	90 (27.1)
Gokak	69	2 (2.9)

**Prevalence varied significantly between the Taluks (P<0.001).*

Table III Risk Estimation for HIV Infection (*N*=509)

Variables	*Odds Ratio*	*95% CI*	*P value*
Unexplained fever	2.64	1.16; 6.02	0.02
Orphan child	305.92	30.99; 3019.98	0.001
Parents with HIV	79.91	32.21; 198.24	0.001

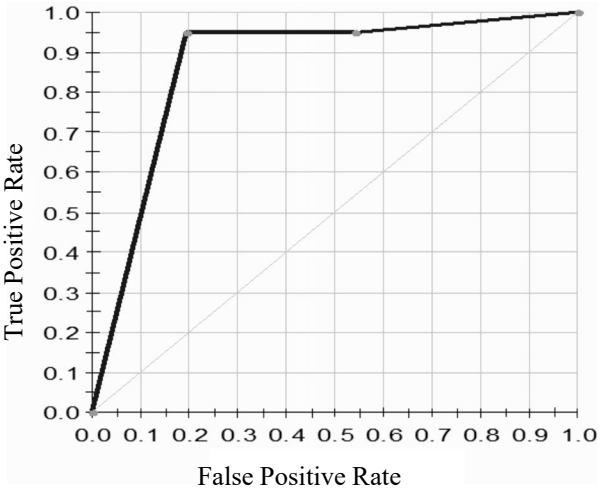

Fig. 1 *Receiver operating characteristic (ROC) curve for identifying children with HIV in the study area.*

prevalence. The modified integrated algorithm can thus be further modified and used to predict pediatric HIV infection in similar settings.

In addition to a binary logistic regression analysis, we performed a CART analysis [14], which is mathematically identical to certain familiar regression techniques, but presents the data in a way that is easily interpreted by those not well versed in statistical analysis. In a large public health project, CART is useful to present preliminary data to clinicians or other project stakeholders who can comment on the statistical results with practice knowledge and intuition. This process yields a well informed and statistically informative model than a singular clinical or statistical approach. The results of CART model and logistics regression model were in agreement and parents with HIV and orphan child had high priority scores with high sensitivity and specificity.

Limitation of the study was lack of validation of the algorithm, which required blood sample collection from children testing negative on the screening tool (questionnaire) in healthcare facilities. Both practitioners and patients resisted blood collection purely for research purposes. A higher prevalence of HIV as reported in the study is expected in the population of sick children. Considering the high proportion (30-40%) of population belonging to 5-14 year age group, policy makers should consider including HIV estimates in routine surveillance until universal coverage becomes a reality.

We conclude that the modified integrated algorithm developed by ICMR can be used as a screening tool in the public and private health care settings to detect pediatric HIV where universal screening for HIV is not yet available/feasible. The important predictors of pediatric HIV infection in settings with low prevalence and yet a high burden, as in many LMICs are parent with HIV, being orphan and unexplained fever more than one month.

Contributor: AS: coordinated the study, conceived the idea, wrote the proposal, monitored study implementation, contributed to statistical analysis, provided critical inputs to the manuscript and approved it; RW and RS were responsible for obtaining and field level compliance for ethics, regulatory and financial approvals, study implementation, data collection, and provided inputs for revising the manuscript; PV: conducted advanced statistical analyses, contributed to the manuscript, reviewed and revised the manuscript; RSP: conducted data analyses, reviewed the draft manuscript; and SI was responsible for regular guidance and support, reviewed the manuscript.
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Web Table I Comparison of CART and Logistic Regression Model by Diagnostic Measures

Diagnostic measures	*CART model*	*Logistic regression*	*95% CI*
Sensitivity (%)	94.0	94.8	88.5-97.8
Specificity (%)	90.0	90.0	86.8-92.6
Diagnostic accuracy (%)	91.0	91.2	88.2-93.2
PPV (%)	69.0	69.4	60.9-76.4
AUC	0.93	0.95	0.94-0.98

PPV: Positive predictive value; AUC: Area under the curve.