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A Drug Utilization Evaluation of Bronchodilators Using a Defined Daily Dose Method

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ABSTRACT:
Drug therapy is crucial to promoting human health by increasing quality of life and extending lifespan. A method to assess and improve drug use is by conducting Drug Utilization Study. Drug utilization, in terms of DDD, aids in converting the available volume of medications into medically relevant units, allowing estimations of the number of people exposed to a certain medicine or class of medicines. A prospective observation study was carried out to assess the consumption of bronchodilators among in-patients. Theophylline was the most utilized bronchodilator with 469.54 DDD/100bed-days. Total consumption of bronchodilators 872.91 DDD/100bed-days. Methylxanthines like Theophylline and Etofylline tablets were over-utilized with PDD:DDD ratio of 4.35 and 3.26 respectively.

Keywords: Drug Utilization Evaluation, Defined Daily Dose, Anatomical Therapeutic Chemical, Prescribed Daily Dose, Bronchodilators.

INTRODUCTION

Drug Utilization Study is a valuable method to evaluate and enhance drug use. It is an effective technique for assessing current trends in drug consumption and the appropriateness of prescriptions. It is a descriptive and analytical strategy for gathering, quantifying, comprehending, and evaluating the prescribing pattern as well as dispensing and consuming for the improvement of current treatment and improvement of patient safety. It describes the extent, type, and determinants of drug exposure, making it a crucial component of pharmacoepidemiology.

Anatomical Therapeutic Chemical (ATC) Classification Code is the most common and practical classification scheme for a drug utilization expression. The ATC system was started by Norwegians Medicinal Depot in the 1970s and is now coordinated by WHO Collaborating Center for Drug Statistics Methodology, founded in 1982 in Oslo.[1] The Center keeps an online database, as well as a printed index, and updates the ATC codes as necessary. Depending on the organ or system in which they work, as well as their therapeutic and chemical qualities, drugs are categorized into a number of distinct classes. Each medicine is assigned at least one ATC code, which is divided into five different levels of groupings. See Table 1 for an illustration using Salbutamol.

Table 1: Classification of Salbutamol using ATC classification system

ATC classification	ATC category	Description
R	Respiratory system	1st level, anatomical main group
R03	Drugs for obstructive airway diseases	2nd level, therapeutic main group
R03C	Adrenergics for systemic use	3rd level, therapeutic/pharmacological subgroup
R03CC	Selective ß2 adrenoreceptor agonist	4th level, chemical/therapeutic/pharmacological subgroup
R03CC02	Salbutamol	5th level, subgroup for chemical substance

The DDD is the anticipated average daily maintenance dosage for an adult medication used for its primary indication whereas the Prescribed Daily Dose (PDD) will provide the average daily dose of a medicine that has been prescribed. The DDD metric system expresses drug use in hospitals as an estimated proportion of patients treated with a certain drug during a specified time period. The DDD's data on drug use only provides an approximate picture of consumption and not a precise representation of real use. ATC/DDD-based pharmacoepidemiological studies provide accurate and consistent comparisons of drug usage within and between nations to enable better outcomes and high-quality use of medications. By analysing drug utilization, some potential issues like overuse, underuse, or misuse of medications can be identified, leading to improved patient safety and cost-effectiveness.As the national burden of respiratory disease rises, so does the use of medications such as bronchodilators in hospitalized patients. Such research aided in the effective management of bronchodilators in the ward.

MATERIALS AND METHODS

This is a prospective observational study conducted in the Department of General Medicine, ESIC MC-PGIMSR, Rajajinagar, Bengaluru, for the period of 6 months. 216 in-patients were enrolled in this study who were prescribed with bronchodilators from March 2022 to August 2022.

INCLUSION CRITERIA

- In-Patients admitted in General Medicine ward of ESIC MC-PGIMSR, Rajajinagar, prescribed with different dosage forms of bronchodilating agents like Short and Long acting β_2-agonist, Short and Long-acting muscarinic antagonist, and Methylxanthine.
- Patients prescribed with mono and /or combination therapy of bronchodilating agents.
- Patients ≥ 18 years of age.
- Patients of any gender.

EXCLUSION CRITERIA

- Lactating and Pregnant women.
- Patients not willing to provide consent.

The patients' demographic and treatment details were collected from the case sheets and medication charts using a self-designed data collection form after obtaining approval from the IEC committee of ESIC MC-PGIMSR. Statistical analysis was performed & DDD/100 bed-days for the various bronchodilating agents was calculated using the formulas.

$$\text{Drug Usage (Defined Daily Dose)}^{[2]} = \frac{\text{Number of items used} \times \text{Amount of drug per item (mg)}}{\text{WHO recommended DDD of drug}}$$

$$\text{DDD/100 bed-days}^{[2]} = \frac{\text{No. of units of drug prescribed during the study period} \times 100}{\text{DDD} \times \text{No. of days in study period} \times \text{No. of beds} \times \text{Bed occupancy}}$$

RESULTS

During the study period, on total 8519 prescriptions were observed and 216 patients who were prescribed with bronchodilating agents were enrolled in our research study from in-patient department of General Medicine ward at ESIC MC- PGIMSR & Model Hospital, Rajajinagar, Bengaluru. An average length of hospital stay days were 9.90, with a deviation of ±5.09 days**.** It was observed that majority of the patients (63.89%) were having hospital stay of 1-10 days, in which males were 35.19% and females were 28.70% (Table 2). Majority of the patients admitted during the study period were in the age group of 50-59 years, n=64 (29.63 %). Majority of the study subjects were males n=126 (58.33%). There were n=90 (41.67%) females in all. The number of smokers n=36 (16.67%) and alcoholics n=36 (16.67%) were same and both were higher than non-smokers, non-alcoholics, ex-smokers & ex-alcoholics. Most common complaints for hospital admission were gastrointestinal issues (n=120), breathlessness (n=106), cough (n=102), fever (n=79), followed by neurological (n=60), musculoskeletal complaints (n=15). During the hospital stay, most of the patients had complaints of cough with expectoration (n=45), breathlessness (n=29) followed by fever, orthopnea as depicted in Figure 1.

Table 2: Distribution of patients on basis of length of hospital stay (in days)

Length of stay (in days)	Males	Females	Total patients	%
1-10	76 (35.19%)	62 (28.70%)	138	63.89
11-20	44 (20.37%)	25 (11.57%)	69	31.94
21-30	6 (2.78%)	3 (1.39%)	9	4.17
Total	**126 (58.34%)**	**90 (41.66%)**	**216**	**100**

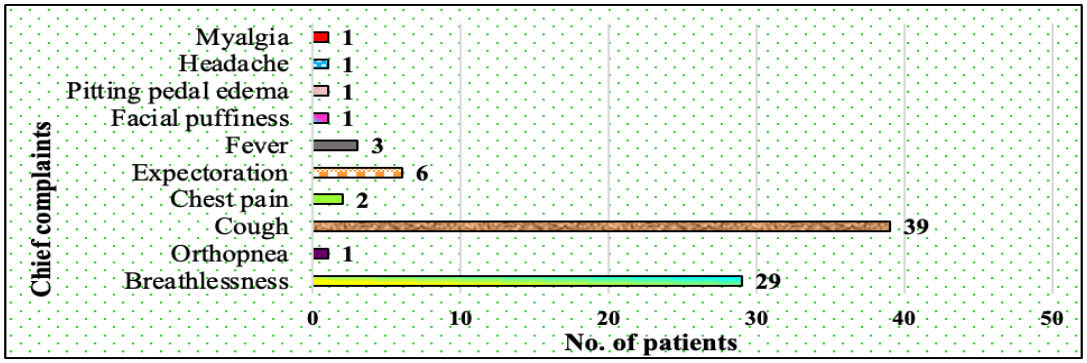

Figure 1: Chief complaints during hospital stay

Hypertension n=79 (36.57%) was found as the major past medical history compared to Diabetes mellitus n=73 (33.80%), COPD n=32 (14.81%). Total 69 patients were not having any past medical history, in which males were n=42 (60.87%) and females were n=27 (39.13%). Majority of the study population were diagnosed with Hypertension (n=68) & Diabetes mellitus (n=68) followed by COPD & Acute Exacerbation of COPD (n=61) as depicted in Figure 2.

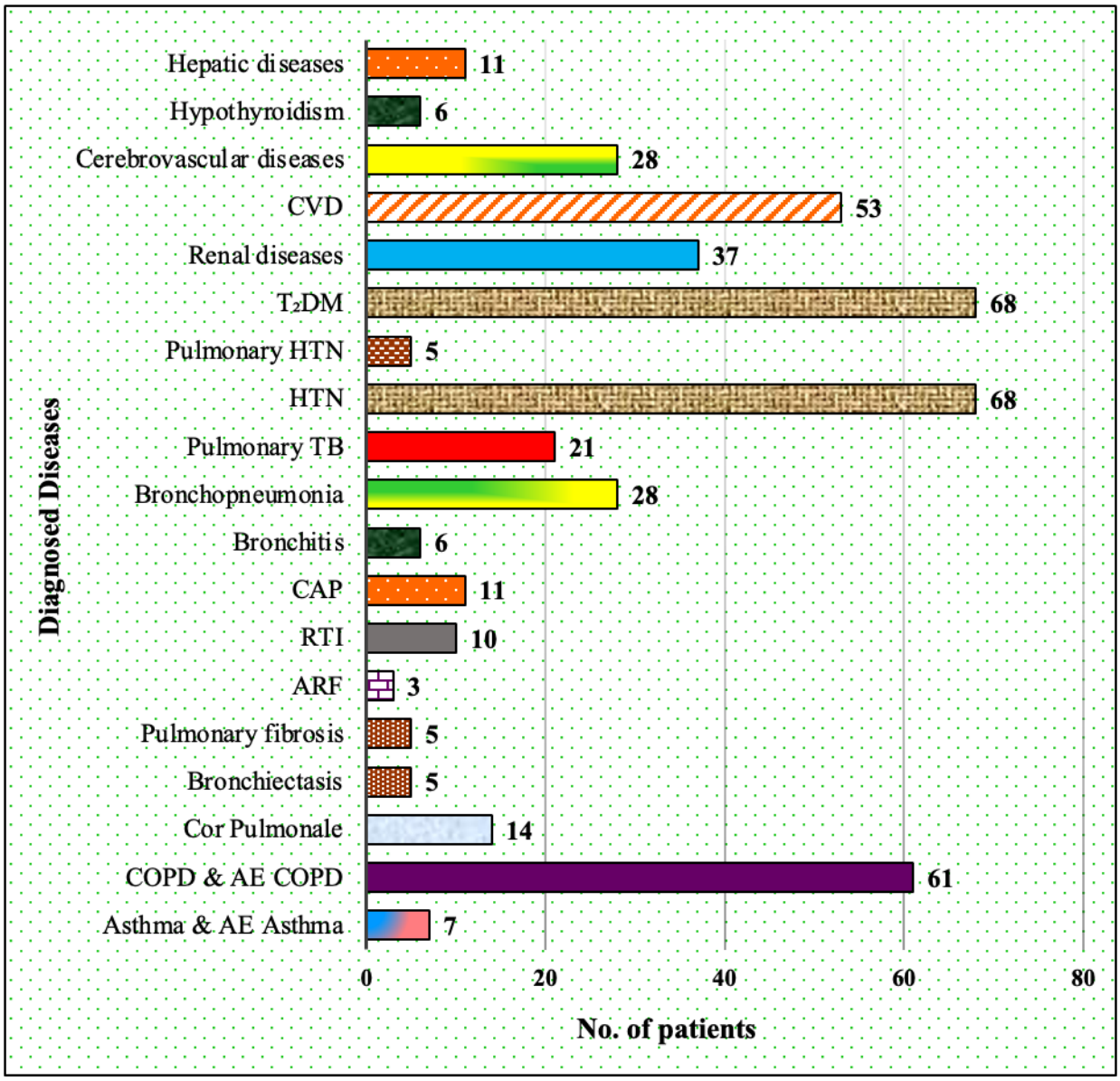

Figure 2: Distribution of patients based on diagnosis

Table 3 contains the different categories of bronchodilating agents, which were commonly prescribed in the ward during the study period.

Categories		Name of the drugs
Selective β_2- adrenergic receptor agonist	Short Acting β_2 - Agonists (SABA)	Terbutaline, Salbutamol
	Long Acting β_2 - Agonists (LABA)	Salmeterol
Methylxanthines		Theophylline, Etofylline

Anti-Cholinergic/ Anti- Muscarinic receptor antagonists	Short-Acting Muscarinic Receptor Antagonists (SAMA)	Ipratropium bromide
	Long-Acting Muscarinic Receptor Antagonists (LAMA)	Tiotropium bromide

It was observed that, Ipratropium bromide with Salbutamol n=158 (44.4%) as FDC was the most commonly prescribed bronchodilating agent as depicted in Table 4.

Table 4: Commonly prescribed bronchodilators

Bronchodilators	Total numbers	%
Salbutamol	20	5.62
Ipratropium bromide	21	5.90
Tiotropium bromide	4	1.12
Terbutaline	120	33.71
Etofylline + Theophylline	20	5.62
Salmeterol + Fluticasone	13	3.65
Ipratropium bromide + Salbutamol	158	44.38
Total	**356**	**100**

Solutions for nebulization n=190 (88%), administered through nasal route were commonly utilized followed by syrups n=121 (56%) which were administered orally as shown in Table 5.

Table 5: Distribution of patients based on dosage forms and routes of administration

Dosage forms	Routes of administration	Drugs	Total patients	Percentage (%) n= 216
Syrup	Oral	Terbutaline	120	55.56
		Salbutamol	1	0.46
Tablet		Etofylline + Theophylline	20	9.2
MDI	Oral Inhalation	Salbutamol	8	3.70
		Tiotropium bromide	4	1.85
		Salmeterol + Fluticasone propionate	13	6.02
Solution for nebulisation	Nasal	Salbutamol	11	5.09
		Ipratropium bromide	21	9.72
		Salbutamol + Ipratropium bromide	158	73.15

Maximum number of drugs per patient were 6 which was found in n = 1 (0.48%) patient while least number of drugs per patient was 1 which was found among 48.80% (n =102) patients as in Table 6.

Table 6: Average number of bronchodilators per patients

Number of drugs per patients	Male	Female	Number of patients	%
1	55	47	102	48.80
2	52	26	78	37.32

3	8	8	16	7.66
4	8	2	10	4.78
5	0	2	2	0.96
6	1	0	1	0.48
Total	**124**	**85**	**209**	**100**

An average number of units of these drugs prescribed per patient was 44.03. SABA as a single therapy, for instance Terbutaline had the highest number of units utilized 4540 (47.74%) while in dual therapy, FDC of SABA with SAMA i.e., Salbutamol with Ipratropium bromide had the highest number of units utilized 3976.8 (41.82%) as in Table 7. This study measured the consumption of bronchodilators over a 3 months period, finding a total consumption of 9509.8 units. Bronchodilators were most commonly utilized in the age group of 50-59 years, n = 65 (30.09%), in which it was utilizes more in males (n = 36) when compared to females (n = 29).

Table 7: Various drug therapies & units utilized for bronchodilating agents

Various drug therapies	Categories	Name of the drugs	Units	%
Single therapy	SABA	Terbutaline	4540	47.74
		Levosalbutamol	21	0.22
		Salbutamol	175	1.84
	LAMA	Tiotropium bromide	51	0.54
	SAMA	Ipratropium bromide	434	4.56
Total single therapy (A)			**5221**	**54.90**
Dual therapy	Methylxanthines	Etophylline + Theophylline	116	1.22
	SABA + SAMA	Salbutamol + Ipratropium romide	3976.8	41.82
	LABA + ICS	Salmeterol + Fluticasone	196	2.06
Total dual therapy (B)			**4288.8**	**45.10**
Total (A+B)			**9509.8**	**100**

During the study, it was observed that 356 drugs were prescribed, in which 12.64% were prescribed as mono therapy and remaining 87.36% were prescribed as combination therapy. Among monotherapy, n=30 (13.95%) drugs were prescribed to males and n=15 (10.64%) drugs were prescribed to females while among combination therapy, n=185 (86.05%) drugs were prescribed to males and n=126 (89.36%) drugs were prescribed to females. Hence drugs were commonly prescribed as combination therapy in both the population. The drugs were categorized according to ATC classification. DDD/100 bed days was calculated using WHO Recommended DDD (Table 8). The highly utilized bronchodilator during the study period in general medicine ward was Theophylline with 469.54 DDD/100 bed days and its PDD:DDD was 4.35. Current study found that the total consumption of bronchodilating agents in the general medicine ward was 872.91 DDD/100 bed days.

Table 8: Bronchodilation consumption using DDD & DDD/100 bed days

Bronchodilating Agents	WHO recommended DDD (mg & UD)	Route	ATC code	Calculated DDD	DDD/100 bed days	PDD	PDD:DDD
Terbutaline	15	Oral	R03AC03	378.33	17.61	61.68	0.16
Salbutamol	12	Oral	R03CC02	1.75	14.09	0.23	0.13
	10	Inhalation (Solution)	R03AC02	18.75	11.74	2.04	0.11
	0.8	Inhalation (Aerosol)		13.38	0.94	0.12	0.01
Ipratropium bromide	0.3	Inhalation (Solution)	R03BB01	723.33	0.35	2.36	0.00
Tiotropium bromide	0.005	Inhalation (Solution)	R03BB04	91.8	0.01	0.00	0.00
Theophylline	400	Oral	R03DA04	17.29	469.54	75.18	4.35
Etofylline nicotinate	300	Oral	C04AD04	77.11	352.15	251.45	3.26
Salbutamol + Ipratropium bromide	3 UD	Inhalation (Solution)	R03AL02	1325.6	6.14	75.32	0.06
Salmeterol + Fluticasone	4 UD	Inhalation (Aerosol)	R03AK06	49	1.29	0.59	0.01

Total of 143 patients were prescribed with discharge medication, in which males were n=85 & females were n=58. Total number of units prescribed were n=424. It was observed that Terbutaline had the higher number of prescribed units (45.99%) in form of syrup and was commonly prescribed to females 19 (13.29%) while Salmeterol with Fluticasone MDI as FDC were commonly prescribed to males 25 (17.48%) as shown in Table 9. Budesonide as MDI and solution for nebulization was prescribed as concomitant drug along with bronchodilating agents. It was mostly prescribed to male 88 (69.84%) followed by female 66 (73.33%) as in Table 10.

Table 9: Distribution of patients based on discharge medicines prescribed

Name of the drugs	Dosage forms	Units	%	Male	Female
Terbutaline	Syrup	195	45.99	21 (14.69%)	19 (13.29%)
Salbutamol + Ipratropium bromide	MDI	27	6.37	9 (6.29 %)	9 (6.29 %)
	Solution for nebulization				
Salbutamol	MDI	27	6.37	14 (9.79%)	5 (3.50 %)
	Solution for nebulization				
Ipratropium bromide	MDI	7	1.65	3 (2.10%)	0
	Solution for nebulization				
Salmeterol + Fluticasone	MDI	144	33.96	25 (17.48%)	16 (11.19%)
Tiotropium bromide	MDI	16	3.77	8 (5.59%)	5 (3.50%)
Etophylline + Theophylline	Tablet	8	1.89	5 (3.50%)	4 (2.80%)

Table 10: Concomitant drugs prescribed along with bronchodilating agents

Drugs	Dosage forms	Male (n=126)	Female (n=90)
Ambroxol Hydrochloride + Guaiphenesin	Syrup	69 (54.76%)	51 (56.67%)
Ambroxol Hydrochloride	Syrup	14 (11.11%)	7 (7.78%)
Ambroxol + N-Acetylcysteine	Tablet	3 (2.38%)	1 (1.11%)
Budesonide	MDI, Solution for nebulization	88 (69.84%)	66 (73.33%)
Hydrocortisone	Injection	30 (23.81%)	20 (22.22%)
Methylprednisolone	Injection	9 (7.14%)	9 (10%)
Prednisolone	Tablet	1 (0.79%)	4 (4.44%)
Dexamethasone	Injection	1 (0.79%)	1 (1.11%)
Pheniramine	Injection	15 (11.90%)	8 (8.89%)
Montelukast Sodium + Levocetirizine	Tablet	41 (32.54%)	23 (25.56%)
Levocetirizine	Tablet	1 (0.79%)	4 (4.44%)
Cetirizine	Tablet	5 (3.97%)	7 (7.78%)
Magnesium Sulphate	Solution for nebulization	2 (1.59%)	0 (0%)
N- Acetylcysteine	Tablet, Solution for nebulization	20 (15.87%)	14 (15.56%)
Pirfenidone	Tablet	0 (0%)	1 (1.11%)
Oxygen inhalation	Via nasal prong, face mask, non-rebreather mask	22 (17.46%)	19 (21.11%)

DISCUSSION & CONCLUSION

DUE is an inexpensive, simple and flexible method to assess the utilization pattern of drugs. Total number of beds in the general medicine ward (male & female) were n=108. The total study population n=216 patients admitted in the in-patient ward of general medicine department had an average length of 9.90 hospital stay days, with a deviation of ±5.09 days, which was high when compared with the study done by *Jhaveri et al*., (2014). The demographic parameters of the patients revealed that the number of male patients were admitted higher during the study period when compared to female population. In the study population, 58.33% were male patients and 41.67% were female patients, and this result was similar to result of the study done by *Sawant MP et al.,* (2017). The average age of the study subjects was found to be 57 ±14.56 years. In our study, 29.63% subjects aged between 50-59 years (middle-aged adults) were admitted more during the study period, which was similar to the result of the study done by *Williams A et al.,* (2011). The number of smokers and alcoholics were same in the study i.e., n=36 (16.67%), both were higher than non-smokers 16 (7.41%), non-alcoholics 18 (8.33%), ex-smokers 11 (30.56%) & ex-alcoholics 13 (36.11%) and this result was similar to the results of the study done by *Sawant MP et al.,* (2017) & *Teli A et al.,* (2020). In comparison to the male population, the female population had the lowest number of smokers (n = 0) and alcoholics (n=1). The most common chief complaints for admission were respiratory system related complaints like breathlessness (n=106), cough with sputum (n=114), & expectoration (n=56). 2.31% of patients came for their follow up treatments & medical procedures like chemotherapy, blood transfusion and to take dose of Injection Elaprase. During the hospital stay, n=84 patients complaints of breathlessness, orthopnea, fever, cough with expectoration, chest pain. A significant number of study population n=73 (33.80%) was known case of T_2DM, in which males were n=37 and females were n=36. These results were similar to the result of the study done by *Sawant MP et al.,* (2017). Patients were also known cases of COPD (n=32, 14.81%), PTB (n=17), bronchial asthma (n=19), bronchopneumonia.

Sawant MP et al., (2017) study revealed that 284 patients, were also prescribed with bronchodilators over a period of four months, which included β_2 agonists like Salbutamol and anticholinergic agents like Ipratropium bromide, which were the most frequently prescribed bronchodilating agents followed by Theophylline. In this study, 158 (73.15%) patients had been prescribed with Ipratropium bromide with Salbutamol as FDC. The total consumption of bronchodilating agents in general medicine ward was measured in DDD/100 bed days. The highly utilized bronchodilator during the study period in general medicine ward was Theophylline with 469.54 DDD/100 bed days, which means that 469.54% of in-patients were receiving 1 DDD of the bronchodilating agents on average daily. When the PDD:DDD ratio is less than one, it indicates underutilization, and when it is greater than one, it indicates overutilization of medications. Current study found that Methylxanthines like Theophylline and Etofylline as tablet were over-utilized with PDD:DDD ratio as 4.35 & 3.26. Apart from being a narrow therapeutic index medicine, they are only bronchodilators accessible in tablet form and can be easily consumed without the discomfort of inhaling.

The drawback of this study was, it was carried-out for a short duration in a single ward of the hospital, which was not an appropriate representation of the population as a whole. A suitable cost analysis study can be performed.

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