Economic aspects of switching from one drug to another

prof. dr Slobodan Janković

Structure of the presentation

- Basic facts about switching from drug to a parallel drug
- Results of published pharmacoeconomics studies about switching
- Methodology of translating results of pharmacoeconomic studies to Serbian milieu
- Bayesian estimate of the translated results
- Mandatory generic substitution
- Consequences of inappropriate parallel drug substitution
- When parallel drug substitution in a hospital should not be done
- Case report
- Conclusions

Switching from a drug to parallel drugs with narrow therapeutic index should not be done

- Although bioequivalent, parallel drugs still do not have the same bioavailability, which may lead to larger fluctuations of steady-state plasma concentrations;
- Patients could be successfully treated with any parallel drug from the very beginning.
- It is switching between parallel drugs that should be avoided in clinical practice,since subtle differences in bioavailability may disturb optimal effect
    - Jankovic SM, Ignjatovic Ristic D. Is bioavailability altered in generic versus brand anticonvulsants? Expert Opin Drug Metab Toxicol. 2015 Mar;11(3):329–32.

Definition of a narrow therapeutic index drug

- When minimal toxic dose is **ONLY TWO TIMES** larger than minimal therapeutic dose, a drug is considered to have narrow therapeutic index.
  - Le Corre P. Bioequivalence and generics of index drugs with narrow therapeutic margins. Presse Med 2010;39(2):169-76.
- Examples:
  - Antiepileptic drugs
  - Oral anticoagulants
  - Immunosuppressants
  - Digoxine
  - Antiarrhytmic drugs

Pharmacoeconomics of switching among parallel drugs

- Switching may negatively impact medication adherence, or lead to poorer clinical outcomes and more adverse events.
- „In some instances, switching accomplished cost savings but did so at increased total cost of care because of increased physician visits or hospitalizations.“
    - Straka RJ, Keohane DJ, Liu LZ. Potential clinical and economic impact of switching branded medications to generics. American journal of therapeutics. 2017 May;24(3):e278-89.

Pharmacoeconomics of switching among parallel drugs

- Helmers et al reported consequencies of switching from more expensive to less expensive parallel antiepileptics
- In large number of patients (n = 33,625) it was shown that total costs of treatment with generics were 25.8% higher, despite lower prices of generic drugs
    - Helmers SL, Paradis PE, Manjunath R, Duh MS, Lafeuille MH, Latrémouille-Viau D, Lefebvre P, Labiner DM. Economic burden associated with the use of generic antiepileptic drugs in the United States. Epilepsy Behav. 2010 Aug; 18(4):437-44.

Pharmacoeconomics of switching among parallel drugs

- In a German study patients switched from one to another parallel risperidone had drop in adherence (more than 5.2%), and increase in number of hospitalizations and visits to psychiatrists – total costs were higher, despite 40% lower prices of preparation of risperidone switched to
    - A pharmaco-economic analysis of patients with schizophrenia switching to generic risperidone involving a possible compliance loss. Treur M, Heeg B, Möller HJ, Schmeding A, van Hout B. BMC Health Serv Res. 2009 Feb 18; 9():32.
- In certain cases, switching from among antihypertensives also increased total costs of treatment, due to „extra clinic visits, additional laboratory tests, and potential hospitalization because of cardiovascular events from uncontrolled hypertension“
    - Effectiveness, safety and cost of drug substitution in hypertension. Johnston A, Stafylas P, Stergiou GS. Br J Clin Pharmacol. 2010 Sep; 70(3):320-34.

Key problems when one wish to use results of a pharmacoeconomic study

- Observational pharmacoeconomic studies are infrequent
- Modelling studies are frequently non-transparent and based on just estimates of input parameters
- Variability of outputs (e.g. ICER, net monetary benefit, differences in costs) is often NOT REPORTED
- Large differences in costs of healthcare services and drugs from country to country resulting with even larger differences in treatment costs

Cost studies of switching from one to another preparation of thyroxine

- Cost increase per 6 months per person in USA after switching from one to another thyroxine, study 1 - $165,00
    - Katz M, Scherger J, Conard S, Montejano L, Chang S. Healthcare costs associated with switching from brand to generic levothyroxine. American health & drug benefits. 2010 Mar;3(2):127-34.
- Cost increase per 6 months per person in USA after switching from one to another thyroxine, study 2 - $375,00
    - Khandelwal N, Johns B, Hepp Z, Castelli-Haley J. The economic impact of switching from Synthroid for the treatment of hypothyroidism. Journal of medical economics. 2018 May 4;21(5):518-24.

Estimate of economic consequences of switching among parallel thyroxines in Serbia

- There are no published studies of switching among parallel thyroxines in Serbia
- For the time being, the only option of estimating consequences of switching among parallel thyroxines in Serbia is use of Bayesian statistics, starting from results of published studies in developed countries, adjusted to Serbian unit costs of drugs and healthcare services
- Algorithm of the estimate:
  - By means of Serbian unit costs to transform cost differences of the published studies to corresponding costs in Serbia, i.e. to make appropriate scaling
  - To use adjusted results of the earliest study to define PRIOR distribution of the cost differences
  - To use adjusted results of the next study to define „SAMPLING“ distribution of the cost differences
  - To use Bayesian statistics to estimate „POSTERIOR“ distribution of the cost differences and calculate from it the most probable values

Adjusting the cost difference for Serbian milieu

- **Cost difference in Serbia (RSD)=(A*C*(F1/F2)+A*D*(G1/G2)+A*E*(H1/H2))*B**

  - A = cost difference in US dollars published in an economic study
  - B = exchange rate US dollar – Serbian dinar (RSD)
  - C, D and E = percent of total costs of treatment with thyroxine made by drugs, hospitalizations and outpatient visits, respectively
  - F1/F2, G1/G2 and H1/H2 = ratios of unit costs of drugs, hospitalizations and outpatient visits, respectively
    - **Source of unit prices: WHO | Country-specific unit costs [Internet]. WHO. [cited 2019 Feb 7]. Available from: https://www.who.int/choice/country/country_specific/en/**

Methodology of the estimate

- For cost difference gamma distribution of probability density is used
- Estimate of alpha and beta parameters of PRIOR and „sampling“ gamma distribution is described in: Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian Data Analysis. 3rd edition, CRC Press, Taylor & Francis Group, USA, 2014.
- Estimate of alpha and beta parameters of „posterior“ distribution is made by multiplying prior gamma density distribution with appropriate likelihood function
    - Fink D. A Compendium of conjugate priors. 1997, 1-47. Dostupno na: https://www.johndcook.com/CompendiumOfConjugatePriors.pdf
- All calculations and graphs are from the calculator „Bayesian statistics“ made in Excel 2016 by the author of this presentation

Data sources for PRIOR and „sampling“ distributions of probability density

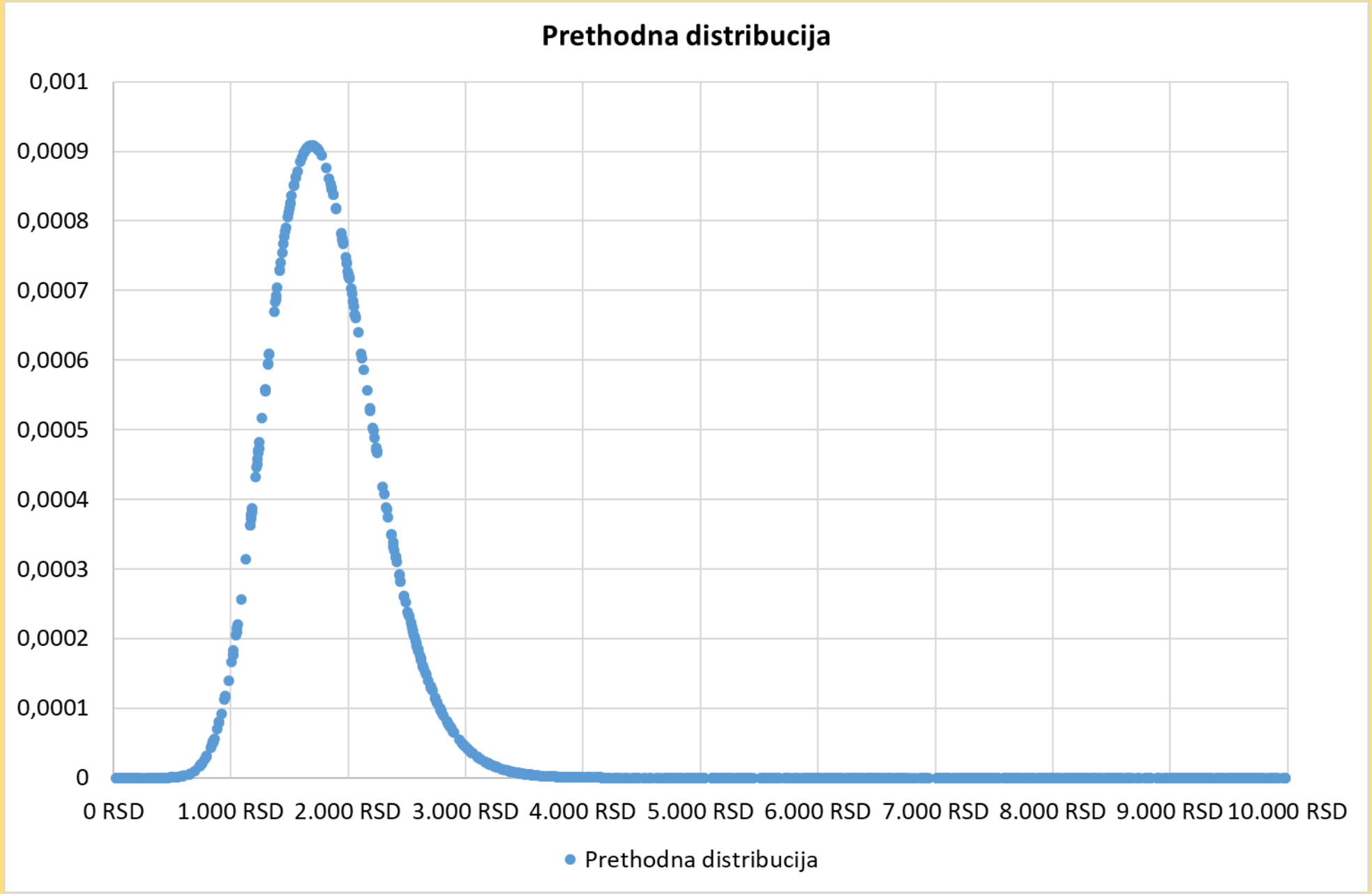
- Katz’s study for PRIOR distribution
- Khandelwal’s study for„sampling“ distribution
- Both studies calculated the cost increase after switching from original to generic thyroxine

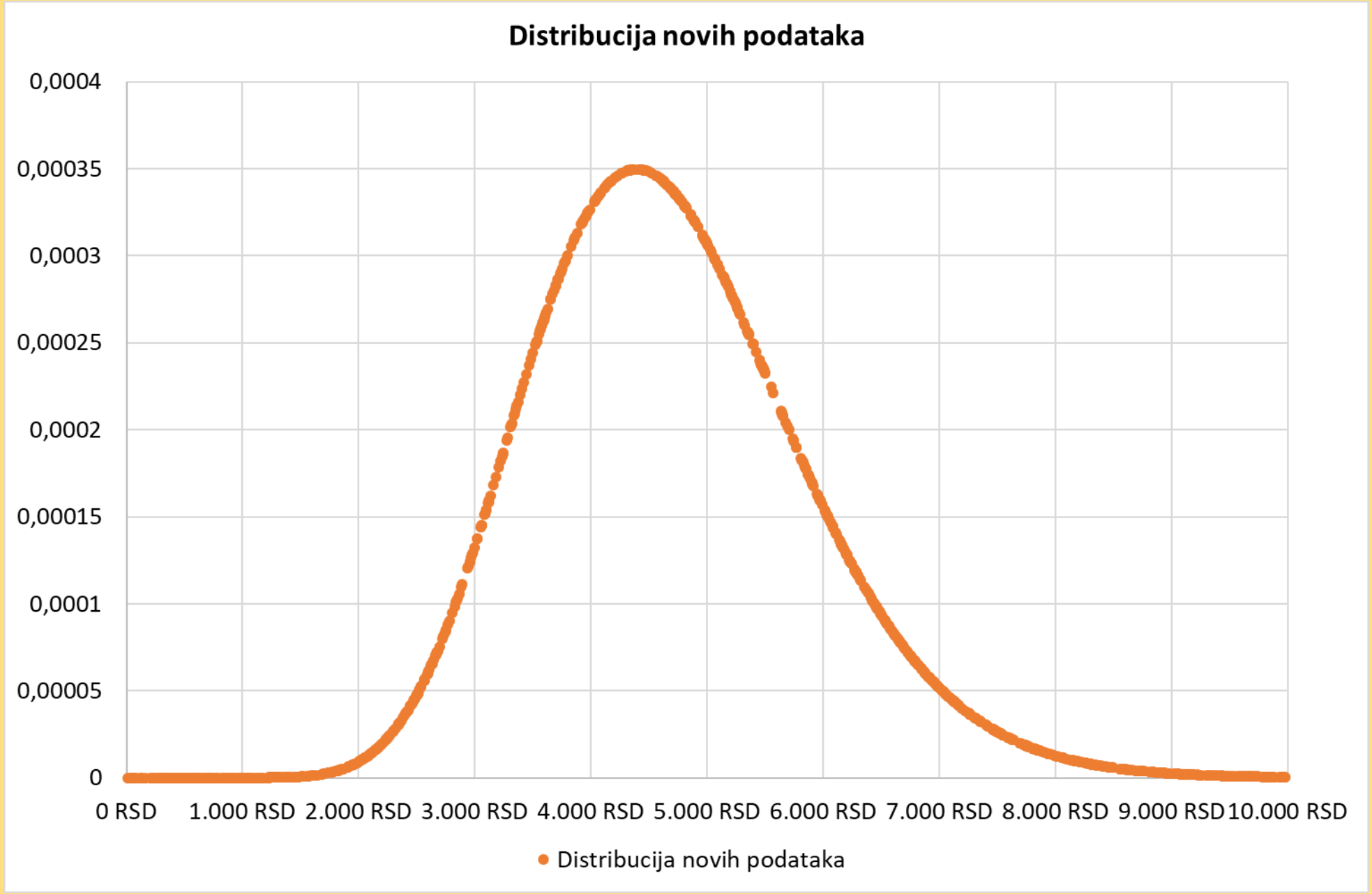
Cena originalnog tiroksina za 6 meseci u USA	$316,00	Katz M, Scherger J, Conard S, Montejano L, Chang S. Healthcare costs associated with switching from brand to generic levothyroxine. American health & drug benefits. 2010 Mar;3(2):127-34.
Cena originalnog tiroksina za 6 meseci u Srbiji	$21,25	Правилник о Листи лекова који се прописују и издају на терет средстава обавезног здравственог осигурања (Службени гласник РС", бр. 43/19 и 55/19 и 56/19-исправка)
Povećanje troškova po pacijentu ako pređe sa originalnog na generički tiroksin - preneto na uslove u Srbiji iz studije 1	1.802,88 RSD	Katz M, Scherger J, Conard S, Montejano L, Chang S. Healthcare costs associated with switching from brand to generic levothyroxine. American health & drug benefits. 2010 Mar;3(2):127-34.
Standardna devijacija povećanja troškova po pacijentu ako pređe sa originalnog na generički tiroksin - preneto na uslove u Srbiji iz studije 1	450,72 RSD	
Povećanje troškova po pacijentu ako pređe sa originalnog na generički tiroksin - preneto na uslove u Srbiji iz studije 2	4.686,59 RSD	Khandelwal N, Johns B, Hepp Z, Castelli-Haley J. The economic impact of switching from Synthroid for the treatment of hypothyroidism. Journal of medical economics. 2018 May 4;21(5):518-24.
Standardna devijacija povećanja troškova po pacijentu ako pređe sa originalnog na generički tiroksin - preneto na uslove u Srbiji iz studije 2	1.171,65 RSD	

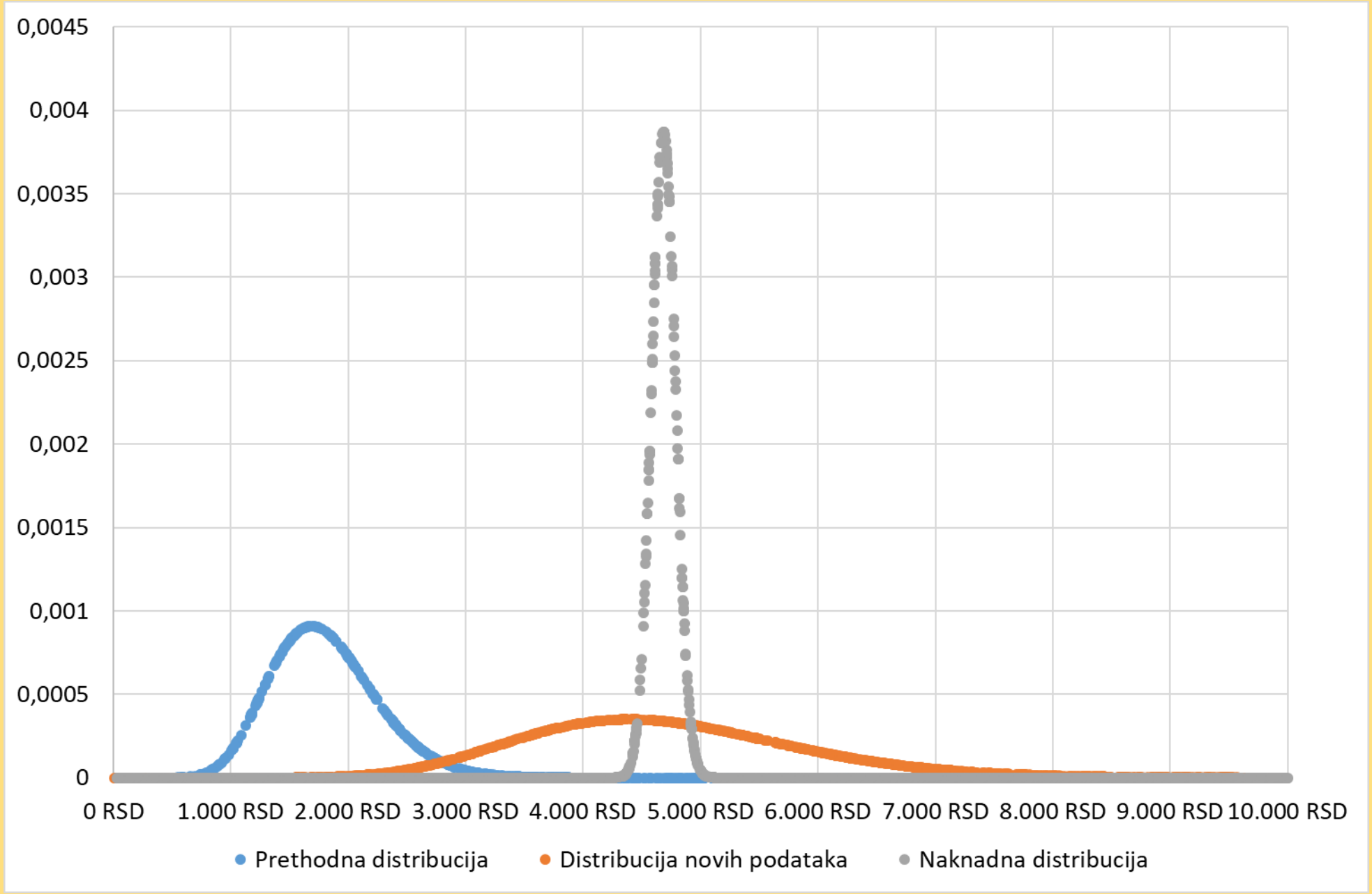
Part of the Bayesian calculator for entering input parameters

			Distribucija novih podataka (n, ȳ, σ)		
	Prethodna gama distribucija (ȳ, σ⊥2), alfa=ȳ²/s^2, beta=s^2/ȳ	**Broj pacijenata u uzorku:**	2052		**Naknadna gama distribucija α +n, β /(1+β*ȳ•v)**
alfa	16,00	**Srednja vrednost u uzorku:**	4686,591984		2068
beta	112,6802386	**Standardna devijacija u uzorku:**	1171,647996		2,266243706
Gama distribucija troškova					

Slučajan broj	Prethodna distribucija	Slučajan broj	Distribucija novih podataka	Slučajan broj	Naknadna distribucija
1491	0,000811817	9626	7,85462E-07	5654	0,000000000000000000045193754910
3051	3,64202E-05	6564	8,72829E-05	1543	0,000000000000000000000000000000


Prethodna distribucija
0,001
0,0009
0,0008
0,0007
0,0006
0,0005
0,0004
0,0003
0,0002
0,0001
0
0 RSD
1.000 RSD
2.000 RSD
3.000 RSD
4.000 RSD
5.000 RSD
6.000 RSD
7.000 RSD
8.000 RSD
9.000 RSD
10.000 RSD
Prethodna distribucija


Distribucija novih podataka
0,0004
0,00035
0,0003
0,00025
0,0002
0,00015
0,0001
0,00005
0
0 RSD
1.000 RSD
2.000 RSD
3.000 RSD
4.000 RSD
5.000 RSD
6.000 RSD
7.000 RSD
8.000 RSD
9.000 RSD
10.000 RSD
Distribucija novih podataka


0,0045
0,004
0,0035
0,003
0,0025
0,002
0,0015
0,001
0,0005
0
0 RSD
1.000 RSD
2.000 RSD
3.000 RSD
4.000 RSD
5.000 RSD
6.000 RSD
7.000 RSD
8.000 RSD
9.000 RSD
10.000 RSD
Prethodna distribucija
Distribucija novih podataka
Naknadna distribucija

Resuts of the Bayesian estimate

The estimate	Cost increase	Confidence interval (99%)
According to the PRIOR distribution of probability density (the first study)	**1,692.00 RSD**	**16.00 – 8,284.94 RSD**
According to the SAMPLING distribution of probability density (the second study)	**4,394.00 RSD**	**14.00 – 9,994.00 RSD**
According to the POSTERIOR distribution of probability density	**4,691.00 RSD**	**0.00 RSD – 5,573.80 RSD**

Conclusions

- Switching among parallel thyroxines in Serbia increases costs of treatment for **4,691.00 RSD (0.00 RSD – 5,573.80 RSD, 99%CI)**
    - 1 GDP per capita in Serbia 2017: 677.178,00 RSD
- The described method is simple, rapid and could involve all published pharmacoeconomic studies through iterative approach: the first posterior distribution could be PRIOR distribution for the next step, and so on, until all published studies are included
    - The iterations could be chronological or according to the sample size (or quality of evidence?)

Mandatory generic substitution

- Mandatory generic substitution of alendronate in Malaysia resulted with increase in adverse drug reactions (OR = 7.84). Patients on brand-name alendronate had adverse drug reactions in 9.4% of cases, while 44.8% of those on generic alendronate had adverse drug reactions
    - Lai PS, Chua SS, Chong YH, Chan SP. The effect of mandatory generic substitution on the safety of alendronate and patients' adherence. Current medical research and opinion. 2012 Aug 1;28(8):1347-55.

List of non-substitutable medicines in South Africa

- The drugs are not-substitutable which:
- i) have a narrow therapeutic range;
- ii) have been known to show erratic intra and inter-patient responses;
- iii) are contained in dosage forms that are likely to give rise to clinically significant bioavailability problems, e.g. extended or delayed release preparations, as well as those known to be super bioavailable; or
- iv) are intended for the critically ill and/or geriatric and paediatric patient.

  - Medicines Control Council of South Africa, Guidelines about Non-Substitutable Medicines, issued in December 2003

Effects of mandatory generic substitution in South Africa

- Only the SSRIs had significant rise in level of generic utilization and a fall in originator usage.
- Utilization of generic PPIs fell, but utilization of originator products also grew.
- Generic calcium antagonists and ACE-I showed an increase in slope, while the originators showed a decrease in slope.

  - Gray AL, Santa-Ana-Tellez Y, J Wirtz V. Impact of the introduction of mandatory generic substitution in South Africa: private sector sales of generic and originator medicines for chronic diseases. Tropical Medicine & International Health. 2016 Dec;21(12):1504-12.

Consequences of inappropriate parallel drug substitution

- Loss of adherence and loss of efficacy
- Increase in adverse drug reactions rate
- Increased costs due to rise in healthcare utilization (more visits to specialists, more hospitalizations...)

Meropenem issue – stability in solution

- Six registered generic preparations in Serbia:
- Preparation 1: stability in solution – 1 hour at room temperature
- Preparation 2: stability in solution – 2 hours at 25^{o}C
- Preparation 3: stability in solution - 2 hours at 25^{o}C
- Preparation 4: stability in solution – 1 hour at room temperature
- Preparation 5: stability in solution - 1 hour at room temperature
- Preparation 6: stability in solution - 3 hours at 25^{o}C
    - Agencija za lekove i medicinska sredstva Srbije, Pretraživanje humanih lekova – Saželi karakteristika meropenema. Dostupno na: https://www.alims.gov.rs/ciril/lekovi/pretrazivanje-humanih-lekova/
- What if a physician wants to maximize meropenem efficacy by prolonging infusion time to 3 hours? Only one generic drug satisfy the condition

A case from practice of a clinical pharmacologist

- 66 years old male patient, suffering from hospital pneumonia
- For 96 hours was receiving meropenem 1g/8h + vancomycin 1g/12h
- Febrile despite the therapy, CRP increasing, white cell count high, Chest X-ray – no improvement
- A clinical pharmacologist consulted
- Generic preparation of meropenem that was used, was then changed for the other and duration of infusion prolonged, with the same dose of 1g/8h
- After next 72h fever disappeared, CRP was halved, white cell count became normal, chest X-ray improved
- The patient was discharged from hospital 10 days later as cured

Conclusions

- Parallel drugs substitution may bring savings to health insurance funds, but only if appropriate
- List of drugs that should not be substituted may prevent adverse consequences of inappropriate substitution
- Inappropriate substitution decreases adherence, increases adverse effects rate and increases total cost of treatment
- Scaling of results of pharmacoeconmic studies from other countries to domestic milieu with Bayesian estimate is helpful when one wants to get an idea of possible changes in costs or cost/effectiveness after switching